

Parkland Manual *of* In-Patient Medicine

An Evidence-Based Approach

Jason N. Katz, Chetan B. Patel, and M. Kamran Aslam



By Residents **For** Residents

Parkland
Manual *of*
In-Patient Medicine
An Evidence-Based Approach

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Parkland Manual *of* In-Patient Medicine An Evidence-Based Approach

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To phenomenal mentors, including L. David Hillis, MD; Mark H. Drazner, MD; Clyde W. Yancy, MD; and the incomparable Daniel W. Foster, MD, who have made the pursuit of medical knowledge so exhilarating, so entertaining, and so gratifying.

To my parents, whose steadfast support has allowed me to pursue all my dreams.

To my wonderful children, Alanna and Aidan, who make each and every day an adventure.

And to my amazing wife, Megan, who shares in my passions no matter how mundane they might be. I am forever indebted to you, and I love you with all my heart.

Jason N. Katz, MD

To my extraordinary mentors who epitomize the lifelong learner and to my peers, the medical house staff of Parkland, who make me better each day. To my parents, for your selfless support of my ambitions. Finally, to my wife, Asha, for your unwavering loyalty and love. I am forever thankful to you all.

Chetan B. Patel, MD

To my creator, the love of my parents, my numerous mentors, and my patients who have positively influenced who I am and who I aspire to be—a “thank you” that will never be enough.

M. Kamran Aslam, MD

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Parkland Memorial Hospital is one of the great teaching hospitals in the nation. Because of this, we have always had a house staff of excellence. We also have a remarkable group of patients. Parkland cares for the medically indigent of Dallas—a very large, uninsured population—with three consequences. First, the population is multiaged, ranging from the young to the very old. Second, because of the wide age span and large number of patients, the variety of diseases represented is remarkable. Third, our patients often delay seeking medical care, with the consequence that critical illness is a constant in the hospital wards and in the intensive care units.

All medical schools teach in both outpatient and inpatient settings, but the balance differs. Our program is weighted toward the hospital. That is deliberate, because the diseases one sees are more concentrated in hospitals. In one sense, Parkland residents were hospitalists decades before “hospitalists” were invented.

The authors of this new manual know about what they write. They do it every day. I am confident that the *Parkland Manual of In-Patient Medicine: An Evidence-Based Approach* will be helpful to all readers seeking quick and reliable advice for hospitalized patients under their care—whether they are students, house officers, or established physicians.

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“Parkland is a hospital where the struggle between life and death, disease and health, is our bread and meat. Rarely a 24-hour period passes that doesn’t bring to our door someone with a story of tragedy, suffering, injustice, or violence. To each of these we offer an outstretched hand—sometimes to care, often to relieve, and always to comfort.”

—Chaplain Kenneth Pepper, in a memorial service for slain President John F. Kennedy

Founded in 1894 by the city of Dallas, Parkland Memorial Hospital was established to provide the highest quality medical care to the indigent sick, working poor, and populations with special needs who would otherwise have minimal access to health services. For over 110 years, Parkland’s pledge to provide medical care to all those in need has never wavered, never faltered. Consistently ranked among the best hospitals in the United States, Parkland is also the primary teaching hospital of the University of Texas Southwestern Medical School, and thousands of physicians have been educated and mentored in the trenches of these historic training grounds.

These physicians-in-training are indebted to Parkland and its patients for providing an unparalleled foundation from which to build prosperous private and academic careers. Some have suggested that any textbook of medicine actually pales in comparison to what can be learned within the walls of this renowned hospital. Based upon this belief, we have developed this manual—a practical, yet comprehensive guide to the acute management of the medical inpatient.

This portable text was designed by the Internal Medicine house staff at Parkland, with support from some of the most outstanding academic faculty in the country. Dissatisfied with the currently available medical handbooks, the resident authors have challenged each other to come up with a practical, fluid, evidence-

based guide that will direct readers seamlessly through the admission, management, and discharge of their patients. Unique in its conception, our manual is designed specifically for residents, fellows, internists, hospitalists, and even specialists. We believe that no one has better insight into the pertinent information that resident physicians need while “on-call” than residents themselves.

Avoiding the prose style that makes other medical manuals inefficient, ours instead uses a functional and succinct “outline-table-algorithm” format, with an accompanying list of differential diagnoses that reference specific sections. We believe this flow of information will make our text more accessible and effective for the busy clinician than any similar book on the market.

While it would be foolish to suggest that our manual is all-encompassing, we have emphasized the frequent use of evidence-based recommendations. Throughout the manual, we have highlighted landmark trials, historical reviews, and the most current data available to support each of the text’s recommendations. We have also utilized consistent levels of evidence to allow the reader to effortlessly pursue any warranted review of the medical literature. Colored icons make interpretation of data easy. References with this icon ❶ represent well-designed prospective, randomized trials and meta-analyses. References with this icon ❷ represent less rigorous prospective and retrospective studies. This icon ❸ highlights general consensus information.

Never has an evidence-based approach to the care of patients been more fundamental to the practice of medicine than it is today. Where other books fail to include appropriate references, and still others overwhelm readers with endless lists of unnecessary and unsubstantiated citations, we believe our manual balances the need for substantive literature support with pure pragmatism.

Another unique aspect of the *Parkland Manual* is its focus on inpatient care. Other manuals of medicine try to incorporate both inpatient and outpatient topics, only to make their product too unwieldy and the information too diluted. We have focused instead only on inpatient topics. The strength of Parkland's Internal Medicine training program is its commitment to exceptional inpatient care, so we have also made that the focus of our manual.

Other unique sections of the *Parkland Manual* include critical care topics, such as ventilator troubleshooting, management of pulmonary arterial catheters and neurological emergencies; indications for emergent bronchoscopy, emergent echocardiography, and renal replacement therapy; differential diagnoses of thoracic radiology; common infectious organisms and their Gram stains; and critical care pharmacology, including dosing, indications, and side effects. In addition, most sections have a "Patient Care Warnings" box that highlights patient safety issues and underscores some of the most important points in the management of specific disease processes.

With its historical perspectives, diagnostic and examination findings, acute management guidelines, troubleshooting tips, and indications for emergent consultation, we hope that the *Parkland Manual of In-Patient Medicine: An Evidence-Based Approach* will be considered the most practical manual on the market—built for clinicians who need concise, evidence-based assistance to manage patients throughout their hospital course. We sincerely hope that you will find this book to be a useful companion as you care for patients throughout your professional life.

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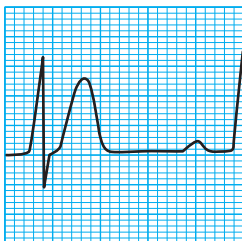
CARDIOLOGY HIGH-YIELD ECG FINDINGS

Rapid interpretation of electrocardiogram (ECG) findings is essential to the effective and efficient practice of inpatient medicine. The following are frequently encountered ECG abnormalities, with descriptions that should help readers in diagnosing and treating their patients.

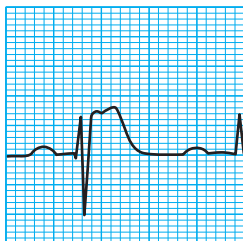
On the following pages, you will find ECG manifestations associated with acute ischemia, cardiac arrhythmias, electrolyte abnormalities, and other common medical conditions.

Myocardial Infarction

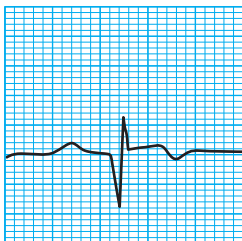
ST segment Elevation MI (STEMI)



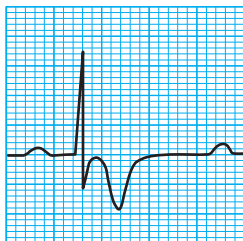
Peaked T waves



ST elevation



Q waves formation



T-wave inversion

Above observed in the natural course of STEMI; in the event of reperfusion, Q wave formation is not a prominent feature

Infarct Location

Lateral MI: ST elevation in Leads I, aVL, V4, V5, V6
(Reciprocal changes in inferior leads)

Inferior MI: ST elevation in Leads II, III, aVF
(Reciprocal changes in anterior and left lateral leads)

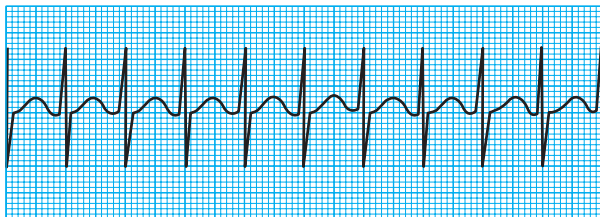
Anterior/Septal MI: ST elevation in greater than two precordial leads (V1-V6) (Reciprocal changes in inferior leads)

Posterior MI: ST depression and tall R wave in V1. ST elevation on right-sided EKG primarily in V4

Non ST-segment Elevation MI (NSTEMI)

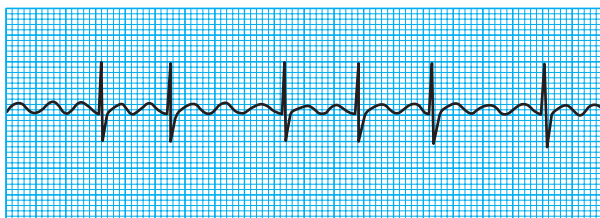
- No ST elevation
- Possible T-wave inversion
- Possible ST-segment depression > 1.0 mm

Supraventricular Arrhythmias



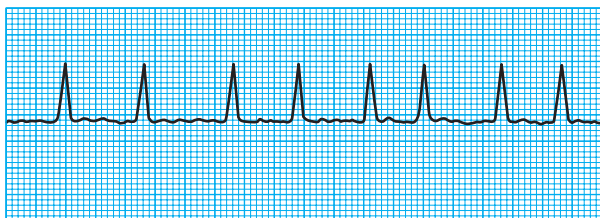
Paroxysmal Supraventricular Tachycardia (PSVT)

- Regular rhythm with ventricular rate of 150–250 bpm
- P wave may be buried within QRS complex or T wave and may not be seen



Atrial Flutter

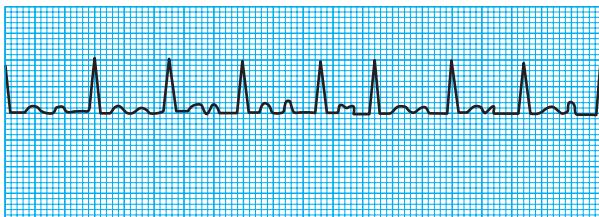
- Regular, sawtoothed pattern with atrial rate of 250–300 bpm
- Variable conduction through the ventricle (2:1, 3:1, 4:1 block)



Atrial Fibrillation

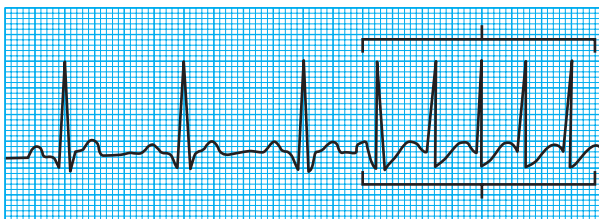
- Irregular with atrial rate of 350–500 bpm
- Variable conduction through the ventricle

Supraventricular Arrhythmias (continued)



Multifocal Atrial Tachycardia (MAT)

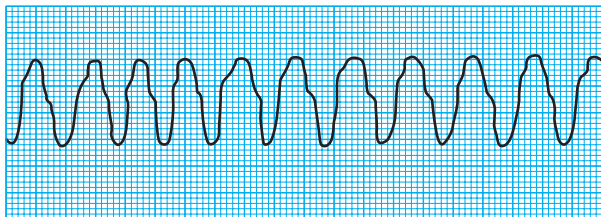
- Irregular rhythm with ventricular rate of 100-200 bpm
- At least 3 different P-wave morphologies



Paroxysmal Atrial Tachycardia (PAT)

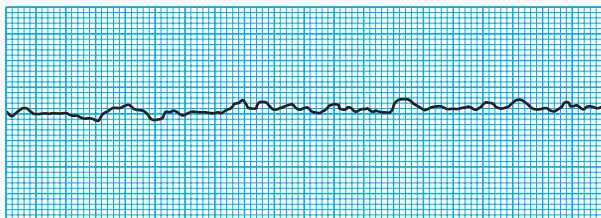
- Regular rhythm with ventricular rate of 100-200 bpm
- Warm-up and cool-down periods more consistent with PAT rather than PSVT

Ventricular Arrhythmias



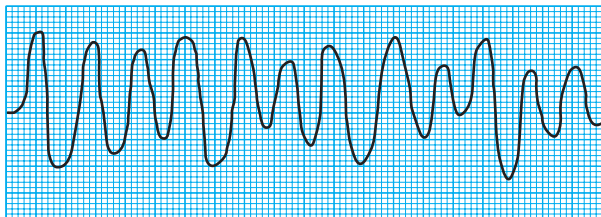
Ventricular Tachycardia (VT)

- 3 or more consecutive ventricular ectopic beats
- Slightly irregular rate between 120-300 bpm
- Monomorphic or polymorphic
- Nonsustained VT (<30 seconds, >100 bpm)
- Sustained VT (>30 seconds, >100 bpm)
- VT may be irregular upon initiation but becomes regular thereafter



Ventricular Fibrillation (VF)

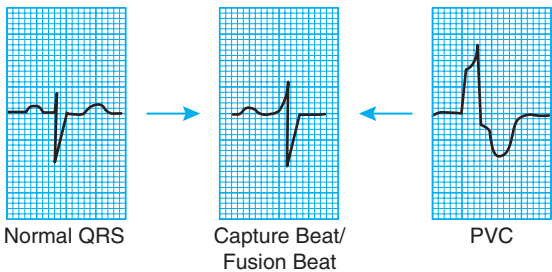
- Baseline chaotic undulation without true QRS complexes



Torsades de Points

- Unique form of VT with the QRS spiraling around a baseline while changing the axis and amplitude

Ventricular Arrhythmias (continued)



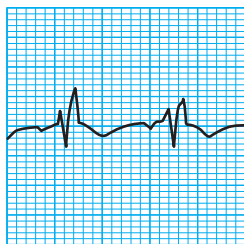
VT vs PSVT: Factors Favoring VT
(Refer to *Wide Complex Tachycardia* for an explanation of the Brugada criteria)

- QRS > 0.14 seconds
- Leftward, rightward, or extreme rightward axis
- AV dissociation
- Precordial concordance
- Absence of RS complex in all the precordial leads
- R to S interval > 100 ms in any precordial lead
- Capture beats or fusion beats

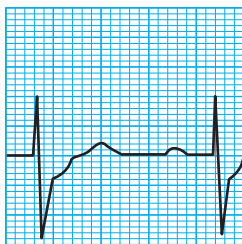
Specific morphologies in the precordial leads

RBBB-like pattern	V ₁ :		V ₆ : R/S ratio < 1
LBBB-like pattern	V ₁ : RT > RS	V2: 1: 30 ms/ 2: notch / 3: 70 ms	V ₆ : qR

Bundle Branch Blocks



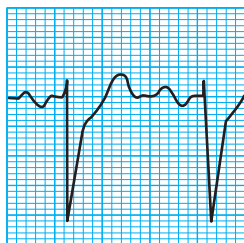
V₁



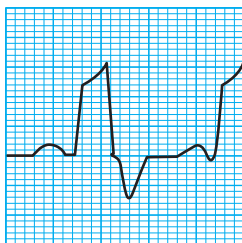
V₆

Right Bundle Branch Block

- QRS > 0.12 seconds
- RSR' (rabbit ears) in V₁ – V₃
- ST depression and T-wave inversion in V₁ – V₃
- Reciprocal changes in V₅, V₆



V₁

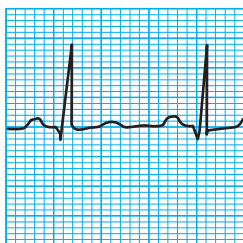


V₆

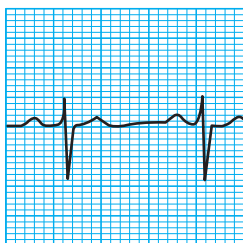
Left Bundle Branch Block

- QRS > 0.12 seconds
- Broad, notched, or slurred R in V₅, V₆, I, AVL
- ST depression and T-wave inversion in V₅, V₆
- Reciprocal changes in V₁, V₂
- Possible LAD

Bundle Branch Blocks (continued)



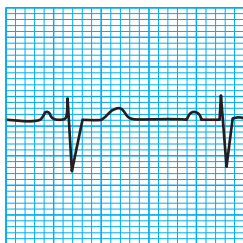
I



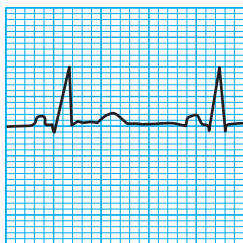
II

Left Anterior Hemiblock

- Normal QRS
- No ST/T-wave changes
- LAD / No other cause of LAD present
- Small R with deep S in II, III, aVF



I



II

Left Posterior Hemiblock

- Normal QRS
- No ST/T-wave changes
- RAD / No other cause of RAD present
- Small R with deep S in I and aVL

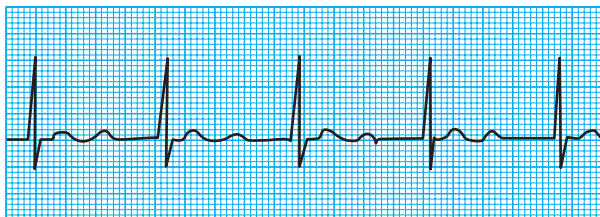
Bifascicular Block

- RBB + LAFB
- RBB + LPFB

Trifascicular Block

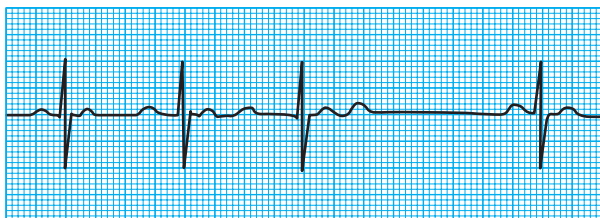
- RBB + LAFB + incomplete AVB
- RBB + LPFB + incomplete AVB

AV Blocks



First Degree AV Block

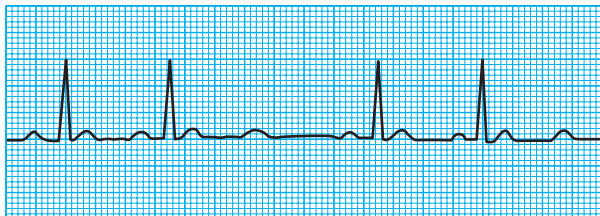
- PR > 0.2 seconds
- All beats conducted



Second Degree AV Block: Mobitz Type I (Wenckebach)

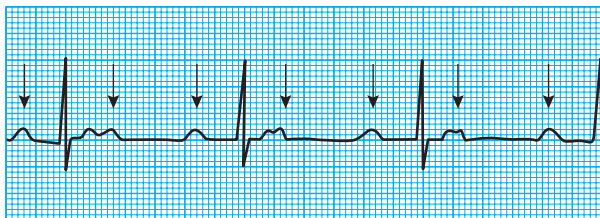
- Progressive PR prolongation followed by dropped QRS complex

AV Blocks (continued)



Second Degree AV Block: Mobitz type II

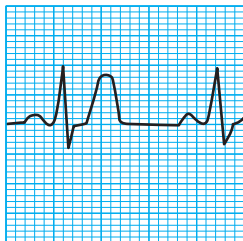
- No PR prolongation
- Randomly dropped QRS complexes



Third Degree AV Block

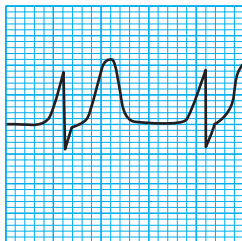
- Complete heart block with AV dissociation
- No ventricular conduction of atrial beats (independent pacemakers)

Electrolytes



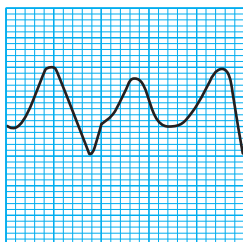
Early Hyperkalemia

- Peaked T wave



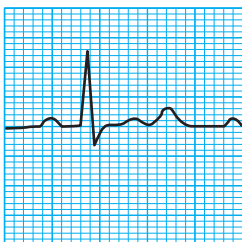
Hyperkalemia

- Prolonged PR
- Flattened P wave
- Widened QRS
- Bradycardia
- First degree AVB



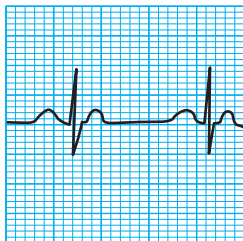
Advanced Hyperkalemia

- SINE wave (QRS and T-wave fusion)



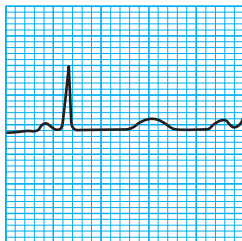
Hypokalemia

- Depressed ST
- Flattened T wave
- U waves



Hypercalcemia

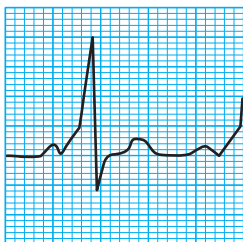
- Shortened QT
- Shortened ST



Hypocalcemia

- Prolonged QT
- Prolonged ST

Miscellaneous



WPW Syndrome

- Wide QRS
- Short PR (<0.12 sec)
- Delta wave (manifestation of fusion beat)



LGL Syndrome

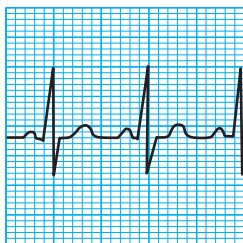
- Normal QRS width
- Short PR (<0.12 sec)
- No delta wave
- Arrhythmias may include PSVT and atrial fibrillation



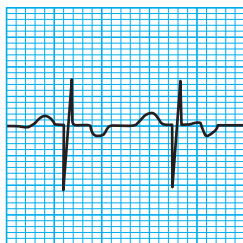
Hypertrophic Obstructive Cardiomyopathy

- LVH with strain
- LAD
- Septal Q waves: V_4-V_6

Miscellaneous (continued)



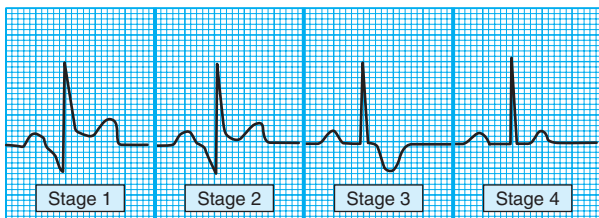
I



III

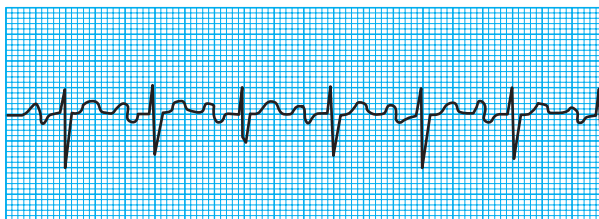
Pulmonary Embolism

- Classic but uncommon: S wave in lead I, Q wave in lead III, T-wave inversion in lead III
- Sinus tachycardia or atrial fibrillation commonly seen
- Large saddle PE: RBBB



Pericarditis

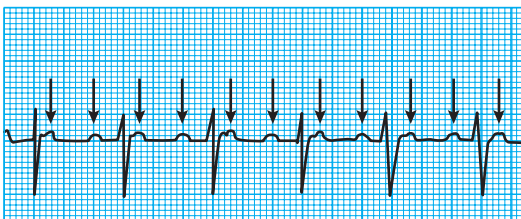
- Stage 1: Diffuse ST elevation / PR depression
- Stage 2: Pseudonormalization (No ST elevation)
- Stage 3: T-wave flattening or inversion
- Stage 4: Normalization



Pericardial Effusion

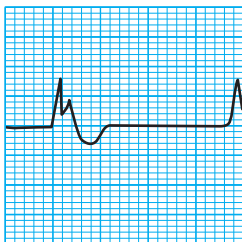
- Low voltage (<5 mm in limb leads, <10 mm in precordial leads)
- Partial electrical alternans present, unless tamponade physiology is present, then total alternans exists

Miscellaneous (continued)



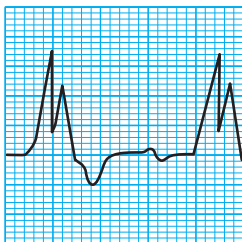
Digitalis Toxicity

- Different combinations of conduction blocks, bradyarrhythmias, and tachyarrhythmias
- First, second, and third degree AVB
- PAT, PVCs, junctional rhythms, atrial fibrillation/flutter
- Most common ECG: PAT with second degree AVB



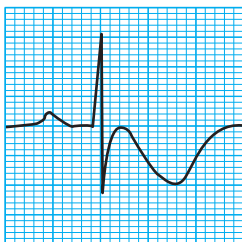
Hypothermia

- Classic: Osborne or J waves - a hump where the QRS complex joins the ST segment
- Common: Sinus bradycardia and prolongation of the PR, QRS, and QT intervals



Myocarditis

- Conduction blocks: Primarily BBB and hemiblocks
- Pericardial effusion



CNS Hemorrhage or Other Disease

- Diffuse T-wave inversion (wide and deep)
- U waves
- QT prolongation

ACUTE CORONARY SYNDROMES AND RISK STRATIFICATION

Definitions, Etiology, and Epidemiology

- Acute coronary syndrome (ACS)¹: clinical symptom constellation compatible with acute myocardial ischemia; spectrum including unstable angina and acute myocardial infarction (AMI)
- Unstable angina (UA)¹: chest pain syndrome without objective evidence of myocardial necrosis, with or without transient electrocardiogram (ECG) changes
 - Early post-MI angina: chest pain occurring within 48 hours following an AMI; usually associated with complex lesions, persistent thrombus, more severe disease,^{2,3} viable myocardium, or a different territory at risk⁴
- Non-ST elevation myocardial infarction (NSTEMI)¹: chest pain syndrome with evidence of cardiac enzyme elevation, with or without ECG changes
- ST elevation myocardial infarction (STEMI)⁵: chest pain syndrome and >0.1 mV ST-segment elevations in contiguous ECG leads
- Etiology
 - Atherosclerosis: lipid deposition and inflammation of the coronary vasculature; this leads to the development of vulnerable plaques which may subsequently rupture and thrombose
 - The cause in $>90\%$ of cases
 - Coronary vasospasm (Prinzmetal angina, cocaine-induced)
 - Syndrome X (MI with normal coronary arteriography)
 - Supply-demand ischemia (increased oxygen demand, reduced coronary blood flow, decreased myocardial oxygen delivery)
 - Coronary vasculitis (polyarteritis nodosa, Takayasu arteritis)

- Degenerative vascular disease (connective tissue disorders)
- Embolism (infective endocarditis, prosthetic cardiac valves)
- Other etiologies of thrombosis (polycythemia vera, hypercoagulable states)
- Trauma (laceration, coronary artery dissection)
- Coronary artery malformations (anomalous coronary origin, myocardial bridge)

Pearls of the History and Physical Examination

History

- Frequency of chest pain
- History of coronary artery disease: previous coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)
- Risk factors for coronary artery disease
- Consider possibility of aortic dissection
- Assess risk of bleeding
- Presence of cerebrovascular disease

Physical Examination

- Heart failure or shock (rales, hypotension, diaphoresis)
- Mechanical complications (new murmurs)

Noninvasive Risk Stratification

Pretest Probability of Coronary Artery Disease

- Pretest probability⁶
 - High: testing may be useful for prognostic purposes; however, a negative test is likely to be a false-negative

- Intermediate: the most likely population of patients to benefit from testing
- Low: positive test likely to be a false-positive; testing not recommended

Testing Modalities

- Exercise electrocardiography
 - Low cost; provides functional and prognostic information
 - Duke Treadmill Score^{7,8}
 - Score = duration of exercise (min) – (5 × max ST-segment deviation during or after exercise [mm] – (4 × angina index)
 - Angina Index = 0 (no angina), 1 (nonlimiting angina), 2 (angina stopped test)
 - High risk (<−10), moderate risk (−10 to +4), low risk (≥+5)

Score	No Stenosis	1 VD	2 VD or Proximal LAD	3 V or LM Disease	5-Year Mortality
Low risk	60%	16%	14%	10%	3.1%
Moderate risk	33%	12%	24%	31%	9.5%
High risk	0.4%	6%	20%	74%	35%

VD = vessel disease; LAD = left anterior descending; LM = left main

- Other testing modalities

Comparison of Risk Stratification Testing^{9,10}

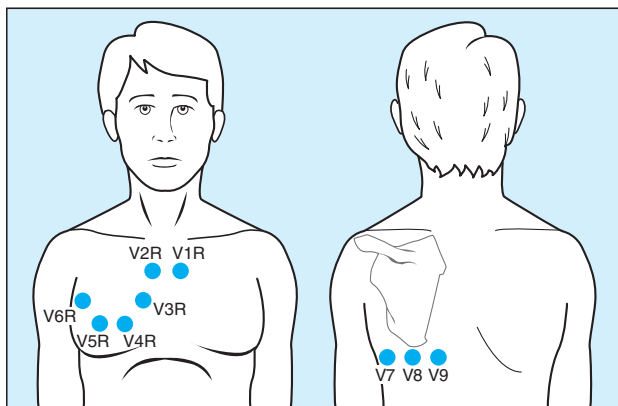
	Sensitivity	Specificity
Exercise treadmill test	68	77
SPECT myocardial perfusion	88	77
Echocardiogram	76	88

- Pharmacological stress should be used if the patient is unable to exercise
 - Vasodilators (results in a relative increase in flow to non-diseased vessels): adenosine, dipyridamole
 - Inotropes (increase myocardial work): dobutamine
 - Imaging should be added in the presence of:
 - Left bundle branch block (LBBB)
 - Paced rhythm, digoxin
 - Pre-excitation conduction abnormalities
 - >0.1 mV resting ST-segment depressions
 - History of revascularization
- Modalities
 - Perfusion imaging
 - Echocardiography

Diagnostic Studies and Laboratory Values

- Chest radiograph: assess for heart failure and aortic dissection
- ECG
 - Less useful for the diagnosis of ischemia with existing LBBB due to associated ST-segment deviations at baseline
 - Right bundle branch block (RBBB), however, is not associated with significant ST-segment deviations
 - ST-segment depressions and T-wave inversions
 - Deep T-wave inversions in precordial leads (Wellens T waves) are specific for proximal left anterior descending (LAD) coronary artery lesions and suggests the need for early angiography
 - ST-segment elevation (>1 mV in at least two contiguous leads)
 - Hyperacute T waves
 - ST elevation
 - Loss of R wave
 - Q wave
 - T-wave inversion

Infarct Localization (Only Useful for ST Elevation Myocardial Infarctions)



	Leads	Coronary Distribution	Associated Infarcts
Inferior	II/III/aVF	RCA, distal circumflex	
Anteroseptal	V ₁ -V ₄	LAD	
Lateral	I/aVL/V5/V ₆	Proximal circumflex	
Right ventricular	V ₁ , V ₄ R	RCA, Circumflex	Inferior (40%)
Posterior	V ₁ -V ₃ (depression) V ₇ -V ₉ (elevation)	RCA, PDA, Circumflex	Lateral and inferior

RCA = right coronary artery; LAD = left anterior descending; PDA = posterior descending artery

- Cardiac biomarkers
 - In cardiac injury, cardiac troponins are more specific than creatine kinase-MB (CK-MB) and are therefore preferred biomarkers for infarction diagnosis and risk stratification; myoglobin elevations are more rapid, but specificity for myocardial damage is low due to confounding factors which

may elevate myoglobin (skeletal muscle damage, cocaine use, renal impairment)

- CK and CK-MB are more helpful in estimating the size of a myocardial infarction
- Thrombolysis in Myocardial Infarction (TIMI) Risk Score for non-ST elevation ACS: a quick measuring tool of patient risk
- Patients with ECG changes or troponin elevations should automatically be considered high-risk patients
- Each criterion counts as 0 or 1
 - Age ≥ 65 , CAD risk factors (family history, diabetes, hypercholesterolemia, current smoker, hypertension); prior angiographically-proven stenosis of $\geq 50\%$; aspirin use within 7 days; more than one episode of rest angina over the past 24 hours; elevated CK-MB and/or troponin; ST-segment deviation (transient ST elevation or ST depression ≥ 0.05)
- Patients with higher cumulative scores appear to benefit from more potent antiplatelet therapy and an early invasive strategy¹¹⁻¹⁴

Guide to Acute Management

Aspirin¹⁵⁻¹⁸

- First medication administered to a patient with suspected myocardial infarction; high benefit, low risk
- 325 mg chewed to rapidly achieve highest blood levels
- Clopidogrel (75 mg daily) can be used if aspirin hypersensitivity or intolerance exists¹⁹

Beta Blockade^{20,21}

- Metoprolol 5 mg IV over 1-2 min every 5 min $\times$ 3 doses, followed by 25-50 mg orally q6h (beginning 15 min after last IV dose)
- Atenolol 5 mg IV, then another dose 10 min later,

followed by 50-100 mg orally daily (beginning 1-2 h after the last IV dose)

- Esmolol 50 $\mu\text{g/kg}$ IV titrated up to 200-300 $\mu\text{g/kg}$

Renin-Angiotensin Blockade^{22,23}

- Angiotensin converting enzyme (ACE) inhibitors are first-line; may consider angiotensin receptor blockers (ARBs) in patients with ACE inhibitor intolerance
- First dose to be given within 24 hours of presentation
- Captopril 6.25 mg titrated to 100 mg/d
- Lisinopril 5 mg, followed by 10 mg/d
- Greatest benefit in those with left ventricular (LV) dysfunction, but likely beneficial in all patients with coronary artery disease

Nitrates

- Sublingual nitroglycerin (SL NTG) 0.4 mg every 5 min
- IV nitroglycerin for ongoing ischemic pain, control of hypertension, or pulmonary congestion; 10 $\mu\text{g/min}$ titrated by 10 $\mu\text{g/min}$ every 3-5 min until symptom or blood pressure response is noted
- Care should be taken in patients who are hypotensive, tachycardic, or who have right ventricular (RV) infarctions
- Nitrates should not be given if there has been exposure to phosphodiesterase inhibitors within the past 24 hours

Morphine Sulfate

- Use when symptoms are not controlled by nitrates, or if pulmonary congestion or agitation is present

Oxygen

- Maintain O_2 saturation $>90\%$

Guide to Directed Management: Unstable Angina (UA) and NSTEMI

Anticoagulation

- Heparin and low molecular weight heparin (LMWH)^{24–27}
- Unfractionated heparin (UFH)
 - More readily reversible
 - Not dependent on renal function
- LMWH
 - No need to monitor
 - Lower incidence of heparin-induced thrombocytopenia
 - At least noninferior to UFH and may have better outcomes in high-risk patients; superior in patients managed conservatively
 - Possible slight increase in risk of bleeding
 - LMWH should not be used in patients with renal failure (creatinine clearance [CrCl] <30 mL/min)
- Direct thrombin inhibitors (hirudin, bivalirudin)²⁸
 - Modest benefit over heparin, with increased incidence of bleeding and increased cost; use in cases of heparin-induced thrombocytopenia (HIT)
- Platelet inhibitors
 - Glycoprotein IIb/IIIa inhibitors^{29–36}
 - High-risk patients
 - Those expected to undergo PCI as it reduces ischemic complications
 - Clopidogrel^{37,38}
 - High-risk patients
 - Those expected to undergo PCI as it reduces thrombotic complications
 - Should be stopped 5–7 days prior to CABG
 - 300–600 mg loading dose, followed by 75 mg/d
 - Duration: 1 month minimum; 3–6 months recommended; consider 1 year (ultimately dependent on type of PCI and stent utilized)

Cardiac Catheterization

- Early invasive strategy: cardiac catheterization within 48 hours of admission
- Early conservative strategy
 - Medical management with above medications
 - If symptoms persist, then pursue angiography
 - If symptom-free, obtain exercise tolerance test (ETT) (consider adjunctive imaging)
 - If ETT negative: continue medical regimen
 - If ETT positive: angiography

Indications for Early Invasive Strategy¹

- Rest angina or angina with low-level activity despite intensive medical treatment
- Angina with signs/symptoms of heart failure
- New ST-segment depression
- Elevated troponin levels
- Hemodynamic instability
- Sustained ventricular tachycardia
- High TIMI risk score
- PCI within 6 months or prior history of CABG
- High-risk findings on noninvasive stress testing (large anterior or multiple defects)
- Noninvasive stress testing with left ventricular ejection fraction (LVEF) <40%
- In the absence of these, early invasive or early conservative strategies may be utilized^{14,39}

Guide to Directed Management: STEMI

Indications for Immediate Reperfusion Therapy

- STEMI within 12 hours of onset (with or without chest pain); this includes posterior infarcts
- STEMI presenting after 12 hours with continuing chest pain
- Myocardial infarction associated with new LBBB

Percutaneous Coronary Intervention

- Preferred over thrombolysis in high-volume centers with experienced operators
- Transfer preferred when PCI is not available if door-to-balloon time transfer will be <90 min⁴⁰
- Adjunctive therapy with glycoprotein IIb/IIIa inhibitors and clopidogrel

Thrombolytics

- Fibrin-specific thrombolytics more effective than non-fibrin-specific thrombolytics
- Similar efficacy with alteplase and bolus reteplase and tenecteplase⁴¹
- Adjunctive therapy with UFH or LMWH with alteplase, reteplase, or tenecteplase
- Absolute contraindications to fibrinolytics (prior intracerebral hemorrhage (ICH), malignant intracranial neoplasm, cerebrovascular malformation, ischemic stroke within 3 months, aortic dissection, active bleeding, closed head/facial trauma within 3 months)
- Clopidogrel prevents reocclusion, recurrent infarction, and reduces mortality

Indications for Surgical Revascularization and Intervention

- Acute infarct in evolution: class I indication in AMI with ischemia refractory to medical therapy, not amenable to PCI, and with suitable anatomy⁴²
- Postinfarction angina: patients with recurrent ischemia or angina on predischARGE stress testing should undergo angiography if not already done
- Indications for CABG include: decreased LVEF; left main disease; diffuse three-vessel disease; single- or two-vessel disease not ideal for PCI, or high-grade proximal LAD lesions^{43,44}

- Mechanical complications of acute MI (see section titled Complications Following Myocardial Infarction)
- Cardiogenic shock (see section titled Complications Following Myocardial Infarction)



Patient Care Warnings

- Beware of post-MI angina
- Check posterior leads with ST-segment depressions in V_{1-3} to rule out true posterior ST-segment elevations
- Avoid nitrates and diuretics in patients with right-sided myocardial infarctions; fluids may be useful
- Be cautious with beta blockers in patients with decompensated heart failure in the setting of MI; may consider esmolol as a test dose
- Therapy in STEMI should not wait for the results of serum biomarkers
- Does your patient have aspirin

References

- ③ 1. Braunwald E, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2000;36:970-1062.
- ② 2. Patel DJ, Gomma AH, Knight CJ, et al. Why is recurrent myocardial ischaemia a predictor of adverse outcome in unstable angina? An observational study of myocardial ischaemia and its relation to coronary anatomy. *Eur Heart J* 2001;22:1991-96.
- ② 3. Bosch X, Theroux P, Waters DD, Pelletier GB, Roy D. Early postinfarction ischemia: Clinical, angiographic, and prognostic significance. *Circulation* 1987;75:988-95.
- ② 4. Schuster EH, Bulkley BH. Early post-infarction angina: Ischemia at a distance and ischemia in the infarct zone. *N Engl J Med* 1981;305:1101-15.

- ③ 5. Antman EM, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2004;110:588-636.
- ③ 6. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;300:1350-58.
- ② 7. Mark DB, Shaw L, Harrell FE Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991;325:849-53.
- ② 8. Shaw LJ, Peterson ED, Shaw LK, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation* 1998;98:1622-30.
- ① 9. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease: A meta-analysis. *Circulation* 1989;80:87-98.
- ① 10. Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Ann Intern Med* 1999;130:719-28.
- ② 11. Morrow DA, Antman EM, Snapinn SM, et al. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes: Application of the TIMI risk score for UA/NSTEMI in PRISM-PLUS. *Eur Heart J* 2002;23:223-29.
- ① 12. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation* 1999;100:1593-1601.
- ① 13. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study investigators. *N Engl J Med*. 1998;338:1488-97.
- ① 14. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)—Thrombolysis in Myocardial Infarction 18 Investigators. *N Engl J Med* 2001;344:1879-87.
- ① 15. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;2:349-60.
- ① 16. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with

unstable coronary artery disease. The RISC Group. *Lancet* 1990;336:827-30.

17. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina: Results of a Canadian multicenter trial. *N Engl J Med* 1985;313:1369-75.
18. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: Results of a Veterans Administration cooperative study. *N Engl J Med* 1983;309:396-403.
19. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348:1329-39.
20. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B study. *Circulation* 1991;83:422-37.
21. Pfisterer M, Cox JL, Granger CB, et al. Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: The GUSTO-I experience. Global Utilization of Streptokinase and TPA (Alteplase) for Occluded Coronary Arteries. *J Am Coll Cardiol* 1998;32:634-40.
22. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995;345:669-85.
23. GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet* 1994;343:1115-22.
24. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999;100:1602-1608.
25. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: A meta-analysis. *Lancet* 2000;355:1936-42.
26. Blazing MA, de Lemos JA, White HD, et al. Safety and efficacy of enoxaparin vs. unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: A randomized controlled trial. A to Z Investigators. *JAMA* 2004;292:55-64.
27. Ferguson JJ, Califf RM, Antman EM, et al. SYNERGY trial investigators: Enoxaparin vs. unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA* 2004;292:45-54.

- 1 28. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: Principal results of a meta-analysis based on individual patients' data. *Lancet* 2002;359:294-302.
- 1 29. Lincoff AM, Califf RM, Anderson KM, et al. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab (c7E3 Fab) among patients with unstable angina undergoing percutaneous coronary revascularization. EPIC Investigators. Evaluation of 7E3 in Preventing Ischemic Complications. *J Am Coll Cardiol* 1997;30:149-56.
- 1 30. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina. The CAPTURE Study. *Lancet* 1997;349:1429-35.
- 1 31. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. *N Engl J Med* 1997;336:1689-96.
- 1 32. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade: Evaluation of platelet IIb/IIIa inhibitor for stenting. The EPISTENT Investigators. *Lancet* 1998;352:87-92.
- 1 33. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. The RESTORE Investigators. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation* 1997;96:1445-53.
- 1 34. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. The PURSUIT Trial Investigators. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression using Integrilin Therapy. *N Engl J Med* 1998;339:436-43.
- 1 35. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 1997;349:1422-28.
- 1 36. ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): A randomised, placebo-controlled trial. Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy. *Lancet* 2000;356:2037-44.
- 1 37. Yusuf S, Zhao F, Mehta SR, et al. Clopidogrel in unstable angina to prevent recurrent events trial investigators: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.
- 1 38. Steinhubl SR, Berger PB, Mann JT, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coro-

- nary intervention: A randomized controlled trial. CREDO Investigators. Clopidogrel for the Reduction of Events During Observation: JAMA 2002;288:2411-20.
- ① 39. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. F Ragmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Lancet 1999;354:708-15.
 - ① 40. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. DANAMI-2 Investigators. N Engl J Med 2003;349:733-42.
 - ① 41. Llevadot J, Giugliano RP, Antman EM. Bolus fibrinolytic therapy in acute myocardial infarction. JAMA 2001;286:442-49.
 - ③ 42. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). J Am Coll Cardiol 2004;44:E1-E211.
 - ① 43. Madsen JK, Grande P, Saunamaki K, et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). DANish trial in Acute Myocardial Infarction. Circulation 1997;96:748-55.
 - ③ 44. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: Executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 1999;100:1016.

COMPLICATIONS FOLLOWING MYOCARDIAL INFARCTION

Definitions, Etiology, and Epidemiology

- Mortality and morbidity rates associated with myocardial infarction (MI) have been steadily decreasing as medical and surgical interventions have improved over the last 30 years
- Complications are secondary to altered physiology

and compromised structural integrity associated with ischemic or infarcted cardiac tissue

- Complications can be categorized into arrhythmias, conduction abnormalities, and mechanical complications; most data are pooled from studies of ST elevation myocardial infarction (STEMI)

Peri-Infarct Arrhythmias¹

Supraventricular	Sinus tachycardia	33% ²	MIs that are large, anterior, associated with LV impairment (higher morbidity, mortality) ²
	Sinus bradycardia	40% ³	Usually with inferior MI (RCA supplies SA node); due to increased vagal tone (Bezold-Jarisch reflex); reperfusion arrhythmia ⁴ ; SA node ischemia ⁵
	Atrial premature beats	15%-30% ³	Harbingers of more severe atrial arrhythmias
	Atrial fibrillation (atrial flutter)	10%-15% ³ (1%-2%) ³	Higher incidence of three-vessel disease ⁶ ; higher 30-day mortality regardless of time of onset ⁷ ; and higher mortality on long-term follow-up (4 years) ⁸
Ventricular	PVCs	93% ⁹	Common; importance is controversial
	VT Early (<48 hours)		PMVT occurs in STEMI (2%-3%), ¹⁰ less in NSTEMI/UA (<1%) ¹¹ ; associated with higher in-hospital and 30-day mortality ^{10,12} ; long-term prognosis unclear ^{10,12,13}

Late (>48 hours)	Predictor of worst prognosis^{10,14}; associated with more complicated in-hospital, posthospital course, and late mortality; probably reflective of development of arrhythmogenic substrate
in NSTEMI	Most data from STEMI; however, sustained VT predicts increased mortality at 30 days and 6 months¹¹
VF	Higher in STEMI^{10,14} compared with NSTEMI/UA¹¹; occurs in the first 48-72 hours,^{10,11,14} and is likely a manifestation of ischemia; associated with increased in-hospital mortality, but not at 1-2 years after discharge^{10,13,14}; hypokalemia (<3.6 mEq/L) associated with early (<4 hours) VF¹⁴
Accelerated idioventricular rhythm	12%-25% Seen by day 2-3; seen equally with inferior and anterior MIs; generally benign unless it degenerates into VT/VF; considered an escape rhythm in circumstance of SN failure

MI = myocardial infarct; LV = left ventricle; RCA = right coronary artery; SA = sinoatrial; PVC = premature ventricular contractions; VT = ventricular tachycardia; PMVT = polymorphic ventricular tachycardia; NSTEMI = non-ST elevation myocardial infarction; UA = unstable angina; VF = ventricular fibrillation; SN = sinus node

Peri-Infarct Conduction Abnormalities

Anterior	AV blocks (below AV node)	1st-degree is rare; 2nd-degree type II; 3rd-degree occurs usually within 24 hours; escape rhythm is wide and unstable due to extensive necrosis of conduction system ¹⁵ and associated with cardiogenic shock ¹⁶
	Left bundle	More common in anterior MI
Inferior	Sinus bradycardia	Most common; see above
	AV blocks (above His bundle)	1st-degree; 2nd-degree type I; 3rd-degree is rare and has narrow QRS escape; more common compared with anterior MI ¹⁶ and associated with increased mortality ¹⁷

AV = atrioventricular

- Conduction abnormalities in anterior MI carry higher mortality than inferior MI
- Conduction abnormalities in inferior MI are usually transient but still increase mortality

Peri-Infarct Mechanical Complications

LV free wall rupture (FWR)	Often occur within first 5 days following infarction; high mortality; more likely with age >70 yr, anterior infarct, no previous ischemic disease, female sex; ST-segment elevations or Q waves on initial electrocardiogram (ECG) ¹⁸⁻²⁰ ; likely due to paucity of collateralization or infarct size; reperfusion decreases risk of FWR ²¹⁻²³ ; generally, incidence of rupture similar in mechanical or medical reperfusion, but mechanical therapy may reduce risk of FWR ¹⁹
Interventricular septum rupture	Within 3-5 days following infarction; high mortality; more likely with single-vessel disease (left anterior descending), large infarct, and poor collaterals ²⁴

Papillary muscle rupture	Within 2-7 days post-MI; posteromedial papillary muscle more commonly affected due to RCA blood supply with minimal redundancy ²⁵ vs. anterior papillary muscle, which has dual supply from the left anterior descending and left circumflex arteries
Right ventricular (RV) infarct	Associated with inferior MI ²⁶ ; majority result from occlusion of the right coronary ²⁷ ; in most, acute RV dysfunction represents ischemic but predominantly viable myocardium ²⁸
LV aneurysm	Result of transmural MI, often anterior; complications include heart failure, thromboembolism, or ventricular arrhythmia ²⁹
LV thrombus	Seen in large, anterior STEMI and in those with post-MI EF <40% ³⁰ usually within first 2 weeks
Cardiogenic shock	Pump failure: LV is the usual culprit, and MI is more often anterior; above mechanical complications can also contribute
Dressler syndrome	See section titled Acute Pericarditis

Pearls of the History and Physical Examination

History

- Sudden death, postinfarction angina, nausea, agitation, anxiety, palpitations, syncope, abrupt hypotension, and respiratory distress

Physical Examination

- New systolic murmur (septal or papillary muscle rupture)
- Precordial thrill (septal rupture)
- Pulmonary edema (shock or papillary muscle rupture)
- Muffled heart sounds, jugular venous distention (FWR)

- Hypotension, jugular venous distention, with clear lung fields (RV infarct)
- Evidence of low cardiac output

Diagnostic Studies and Laboratory Values

- ECG or active telemetry
 - Look for changes compared with admission 12-lead ECG
 - Malignant arrhythmias and electromechanical dissociation
 - With inferior wall ischemia (leads II, III, and aVF), obtain right-sided leads V₄R, V₅R, and V₆R (class I ACC/AHA 2004)³¹ if suspecting RV infarct
 - ST-segment elevation, especially in V₄R, supports acute right ventricular infarction
- Echocardiogram
 - Key diagnostic tool to help diagnose the major mechanical complications; see section titled Indications for Emergent Echocardiography
- Swan-Ganz (pulmonary artery) catheterization with measurement of pulmonary capillary wedge pressure (PCWP) when etiology of shock or cardiac function is unclear
 - Septal rupture: an oxygen step up will be noted
 - Right ventricular infarct: right atrial pressure (RAP) ≥ 10 mm Hg³² and ratio of RAP to PCWP >0.8 (hemodynamically significant infarct)

Guide to Acute Management

Arrhythmia

- Sinus tachycardia: treat underlying cause
- Sinus bradycardia: if manifestations of low cardiac output persist, atropine (up to 3 mg IV), then temporary cardiac pacing if atropine fails^{33,34}
- Atrial premature beats: no specific therapy
- Atrial fibrillation/flutter: see section titled Atrial Fibrillation and Flutter

- In hemodynamic compromise, start with synchronized monophasic DCCV initially with 200 J for fibrillation or 50 J for flutter; if this fails, IV amiodarone or digoxin should be considered
- PVCs: no treatment, unless frequency causes hemodynamic compromise
- VT: Begin advanced cardiac life support (ACLS) protocol
- VF: Begin ACLS protocol

Conduction Abnormalities

- Transvenous (TV) pacing: access approaches recommended for TV pacing include right internal jugular or left subclavian (operator-dependant)

Class I Indications for Temporary TV Pacing in Acute Myocardial Infarction (AMI)³⁵

• Asystole	• Bilateral BBB (alternating LBBB/RBBB or RBBB with alternating LAFB/LPFB of any age)
• 3rd-degree heart block	
• 2nd-degree type II	
• Symptomatic bradycardia (sinus bradycardia with hypotension or atropine-unresponsive 1st-degree AV block with associated hypotension)	• New or age indeterminate bifascicular block (RBBB with LAFB/LPFB or LBBB with 1st degree)

BBB = bundle branch block; LBBB = left BBB; RBBB = right BBB; AFB = anterior fascicular block; PFB = posterior fascicular block; LAFB = left anterior fascicular block; LPFB = left posterior fascicular block

Mechanical Complications

- Class I indications for surgical repair of mechanical defects after MI³⁵
 - Papillary muscle rupture with severe acute mitral insufficiency
 - Postinfarction ventriculoseptal defect or FWR
 - Postinfarction ventricular aneurysm associated with intractable ventricular tachyarrhythmia or significant LV dysfunction

- LV FWR: maintain cardiac output³⁶
 - Emergent surgery is indicated; medical stabilization pending surgery:
 - Rapid colloid fluid infusion and dobutamine at 5-10 $\mu\text{g/kg/min}$
 - Limited pericardiocentesis (10-50 mL); if hypotension and low cardiac output persist, repeat
 - If stabilization occurs, start progressive withdrawal of dobutamine; start beta blockers as tolerated with goal systolic of 100-120 mm Hg, concurrent with prolonged rest; avoid increased intrathoracic pressure; serial echocardiography (every 2-3 days if necessary)
 - May use intra-aortic balloon pump (IABP) to improve hemodynamics and decrease LV afterload
- Interventricular septal rupture: reduce LV workload and therefore degree of shunt; immediate vs. delayed management has been controversial;^{37,38} generally, earlier surgical intervention seems to have better outcomes³⁹
 - Stabilize: reduce afterload with IABP and vasodilators; improve cardiac output with inotropic support³⁹
 - Define coronary anatomy, followed by surgical repair³⁹; concomitant coronary artery bypass graft (CABG) may improve long-term survival⁴⁰
- Papillary muscle rupture: afterload reduction with vasodilators, diuretics, and IABP if needed, thus increasing forward flow and decreasing regurgitant fraction
- RVI
 - Intravenous isotonic fluid resuscitation (normal saline)³¹ to a pulmonary capillary wedge pressure (PCWP) of 15³² or with close monitoring of blood pressure, lung examination, and urine output in the absence of a PA catheter
 - Avoid drugs (diuretics, nitrates) or maneuvers (Foley insertion) that decrease preload

- Decrease RV afterload: be judicious with high positive end-expiratory pressure (PEEP) in ventilated patients; use an IABP³¹ in patients with significant LV dysfunction
- If fluid resuscitation is unsuccessful, dobutamine can be initiated at 5 $\mu\text{g/kg/minute}$ with careful hemodynamic and telemetry^{31,32}
- RV performance can spontaneously improve without reperfusion, but reperfusion can enhance recovery and improve clinical course²⁸; reperfusion not as well studied in RV infarction as left ventricular infarction, and early versus delayed-invasive strategies have not been extensively investigated⁴¹
 - PCI reperfusion reduces mortality, can enhance RV recovery,⁴²⁻⁴⁴ and may be superior to thrombolysis
 - Reperfusion indications are similar to those for left ventricular MI; early reperfusion for right ventricular MI has been given class I recommendation in the ACC/AHA 2004 guidelines³¹ (see Ischemic Heart Disease)
- Left ventricular thrombus
 - Generally, it can be stated that a mural thrombus after AMI has a significant risk for embolization, which can be reduced by systemic anticoagulation for 6 months⁴⁵
 - One study demonstrated that 10 days of 12,500 units q 12 hours of subcutaneous unfractionated heparin was superior to 5000 units q 12 hours in preventing thrombus formation in patients with anterior AMI⁴⁶
 - Low molecular weight heparin (LMWH):
Dalteparin (150 IU/kg SC q 12h) in the setting of an anterior MI significantly reduces LV thrombus formation with an increased risk of hemorrhage⁴⁷;
Enoxaparin (100 IU/kg SC q 12h) in patients with an anterior MI and LV thrombus was well toler-

ated and resulted in reduced echocardiographic thrombus size at a mean follow-up of 13 days⁴⁸

- Cardiogenic shock: see section titled Congestive Heart Failure and Systolic Dysfunction
 - General principles of AMI management apply in cardiogenic shock: aspirin, heparin, and glycoprotein IIB/IIIA inhibitors; special attention should be given to tissue perfusion, which can be augmented by inotropes and vasopressors
 - IABP: improves coronary perfusion and reduces myocardial workload and therefore ischemia (see section titled Intra-Aortic Balloon Pumps).
 - SHOCK trial demonstrated that early revascularization (defined as PCI or CABG) should be pursued in patients with cardiogenic shock complicating AMI, especially as it showed significant survival benefit at 6 months⁴⁹
- Dressler syndrome: see the section titled Acute Pericarditis



Patient Care Warnings

- Beware of AV block in anterior MIs: these may be atropine-unresponsive and therefore require pacing
- Have high index of suspicion for mechanical complications
- Utilize IABPs in cardiogenic shock early in course when indicated

References

- ③ 1. Chizner MS. Bedside diagnosis of the acute myocardial infarction and its complications. *Curr Prob Cardiol* 1982;7:1-86.
- ① 2. Crimm A, Severance H, Coffey K, et al. Prognostic significance of isolated sinus tachycardia during first three days of acute myocardial infarction. *Am J Med* 1984;76:983-88.

- ③ 3. Weinreich D, Michelson E. Arrhythmias during acute MI. 2: Tachycardias, fibrillation and flutter. *Prim Cardiol* 1984;51-63.
- ② 4. Goldberg S, Greenspon A, Urban P, et al. Reperfusion arrhythmia: A marker of restoration of antegrade flow during intracoronary thrombolysis for acute myocardial infarction. *Am Heart J* 1983;105:26-32.
- ③ 5. Chait L. Management of bradyarrhythmias in acute myocardial infarction. *Pract Cardiol* 1981;7:70-8.
- ① 6. Crenshaw B, Ward S, Granger C, et al. Atrial fibrillation in the setting of acute myocardial infarction: The GUSTO-I experience. *Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. J Am Coll Cardiol* 1997;30:406-13.
- ① 7. Wong C, White H, Wilcox R, et al. New atrial fibrillation after acute myocardial infarction independently predicts death: The GUSTO-III experience. *Am Heart J* 2000;140:878-85.
- ① 8. Pizzetti F, Turazza F, Franzosi M, et al. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: The GISSI-3 data. *Heart* 2001;86:527-32.
- ③ 9. Bigger JT Jr, Dresdale FJ, Heissenbuttel RH, et al. Ventricular arrhythmias in ischemic heart disease: Mechanism, prevalence, significance, and management. *Prog Cardiovasc Dis* 1977;19:255.
- ① 10. Newby K, Thompson T, Stebbins A, et al. Sustained ventricular arrhythmias in patients receiving thrombolytic therapy: Incidence and outcomes. The GUSTO Investigators. *Circulation* 1998;98:2567-73.
- ① 11. Al-Khatib S, Granger C, Huang Y, et al. Sustained ventricular arrhythmias among patients with acute coronary syndromes with no ST-segment elevation: Incidence, predictors, and outcomes. *Circulation* 2002;106:309-12.
- ① 12. Eldar M, Sievner Z, Goldbourt U, et al. Primary ventricular tachycardia in acute myocardial infarction: Clinical characteristics and mortality. The SPRINT Study Group. *Ann Intern Med* 1992;117:31-6.
- ① 13. Berger PB, Ruocco NA, Ryan TJ, et al. Incidence and significance of ventricular tachycardia and fibrillation in the absence of hypotension or heart failure in acute myocardial infarction treated with recombinant tissue-type plasminogen activator: Results from the Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial. *J Am Coll Cardiol* 1993;22:1773-79.
- ① 14. Volpi A, Cavalli A, Turato R, et al. Incidence and short-term prognosis of late sustained ventricular tachycardia after myocardial infarction: Results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) Data Base. *Am Heart J* 2001;142:87-92.
- ③ 15. Mullins C, Atkins J. Prognoses and management of ventricular conduction blocks in acute myocardial infarctions. *Mod Concepts Cardiovasc Dis* 1976;45:129-33.
- ① 16. Aplin M, Engstrom T, Vejlstrup NG, et al. Prognostic importance of complete atrioventricular block complicating acute

- myocardial infarction. TRACE Study Group. *Am J Cardiol* 2003;92:853-56.
- ② 17. Behar S, Zissman E, Zion M, et al. Complete atrioventricular block complicating inferior acute wall myocardial infarction: short- and long-term prognosis. *Am Heart J* 1993;125:1622-27.
 - ① 18. Pohjola-Sintonen S, Muller J, Stone P, et al. Ventricular septal and free wall rupture complicating acute myocardial infarction: Experience in the multicenter investigation of limitation of infarct size. *Am Heart J* 1989;117:809-18.
 - ① 19. Moreno R, Lopez-Sendon J, Garcia E, et al. Primary angioplasty reduces the risk of left ventricular free wall rupture compared with thrombolysis in patients with acute myocardial infarction. *J Am Coll Cardiol* 2002;39:598-603.
 - ① 20. Becker R, Hochman J, Cannon C, et al. Fatal cardiac rupture among patients treated with thrombolytic agents and adjunctive thrombin antagonists: Observations from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study. *J Am Coll Cardiol* 1999;33:479-87.
 - ① 21. Honan M, Harrell F, Reimer K, et al. Cardiac rupture, mortality and the timing of thrombolytic therapy: A meta-analysis. *J Am Coll Cardiol* 1990;16:359-67.
 - ① 22. Gertz S, Kragel A, Kalan J, et al. Comparison of coronary and myocardial morphologic findings in patients with and without thrombolytic therapy during fatal first acute myocardial infarction. The TIMI Investigators. *Am J Cardiol* 1990;66:904-909.
 - ① 23. Becker R, Charlesworth A, Wilcox R, et al. Cardiac rupture associated with thrombolytic therapy: Impact of time to treatment in the Late Assessment of Thrombolytic Efficacy (LATE) study. *J Am Coll Cardiol* 1995;25:1063-68.
 - ② 24. Skehan JD, Carey C, Norrell MS, et al. Patterns of coronary artery disease in post-infarction ventricular septal rupture. *Br Heart J* 1989;62:268-72.
 - ③ 25. Estes E Jr, Dalton F, Entman M, et al. The anatomy and blood supply of the papillary muscles of the left ventricle. *Am Heart J* 1966;71:356-62.
 - ③ 26. Kinch JW, Ryan TJ. Right ventricular infarction. *N Engl J Med* 1994;330:1211-17.
 - ② 27. Bowers TR, O'Neill WW, Pica M, et al. Patterns of coronary compromise resulting in acute right ventricular ischemic dysfunction. *Circulation* 2002;106:1104-1109.
 - ③ 28. Goldstein JA. Pathophysiology and management of right heart ischemia. *J Am Coll Cardiol* 2002;40:841-53.
 - ③ 29. Ba'albaki H, Clements SD Jr. Left ventricular aneurysm: A review. *Clin Cardiol* 1989;12:5-13.
 - ① 30. Chiarella F, Santoro E, Domenicucci S, et al. PredischARGE two-dimensional echocardiographic evaluation of left ventricular thrombosis after acute myocardial infarction in the GISSI-3 study. *Am J Cardiol* 1998;81:822-27.
 - ③ 31. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guide-

- lines for the management of patients with ST-elevation myocardial infarction—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004;110:588.
- ① 32. Ferrario M, Poli A, Previtali M, et al. Hemodynamics of volume loading compared with dobutamine in severe right ventricular infarction. *Am J Cardiol* 1994;74:329-33.
 - ③ 33. Rosenfeld LE. Bradyarrhythmias, abnormalities of conduction, and indications for pacing in acute myocardial infarction. *Cardiol Clin* 1988;6:49-61.
 - ② 34. Murphy P, Morton P, Murtagh JG, et al. Hemodynamic effects of different temporary pacing modes for the management of bradycardias complicating acute myocardial infarction. *Pacing Clin Electrophysiol* 1992;15:391-96.
 - ③ 35. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction—executive summary and recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1999; 100:1016.
 - ③ 36. Figueras J, Cortadellas J, Soler-Soler J. Left ventricular free wall rupture: Clinical presentation and management. *Heart* 2000;83:499-504.
 - ② 37. Norell MS, Gershlick AH, Pillai R, et al. Ventricular septal rupture complicating myocardial infarction: Is earlier surgery justified? *Eur Heart J* 1987;8:1281-86.
 - ② 38. Honey M, Belcher JR, Hasan M, et al. Successful early repair of acquired ventricular septal defect after myocardial infarction. *Br Heart J* 1967;29:453.
 - ③ 39. Murday, A. Optimal management of acute ventricular septal rupture. *Heart* 2003;89:1462-66.
 - ② 40. Muehrcke DD, Daggett WM Jr, Buckley MJ, et al. Postinfarct ventricular septal defect repair: Effect of coronary artery bypass grafting. *Ann Thorac Surg* 1992;54:876-82; discussion 882-83.
 - ② 41. Lupi-Herrera E, Lasses LA, Cosio-Aranda J, et al. Acute right ventricular infarction: Clinical spectrum, results of reperfusion therapy and short-term prognosis. *Coron Artery Dis* 2002;13:57-64.
 - ② 42. Kinn JW, Ajluni SC, Samyn JG, et al. Rapid hemodynamic improvement after reperfusion during right ventricular infarction. *J Am Coll Cardiol* 1995;26:1230-34.
 - ② 43. Bowers TR, O'Neill WW, Grines C, et al. Effect of reperfusion on biventricular function and survival after right ventricular infarction. *N Engl J Med* 1998;338:933-40.
 - ② 44. Giannitsis E, Hartmann F, Wiegand U, et al. Clinical and angiographic outcome of patients with acute inferior myocardial infarction. *Z Kardiol* 2000;89:28-35.

- ① 45. Vaitkus PT, Barnathan ES. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: A meta-analysis. *J Am Coll Cardiol* 1993;22:1004-1009.
- ① 46. Turpie AG, Robinson JG, Doyle DJ, et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989;320:352-57.
- ① 47. Kontny F, Dale J, Abildgaard U, et al. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute anterior myocardial infarction. The FRagmin in Acute Myocardial Infarction (FRAMI) study. *J Am Coll Cardiol* 1997;30:962-69.
- ① 48. Meurin P, Tabet JY, Renaud N, et al. Treatment of left ventricular thrombi with a low molecular weight heparin. *Int J Cardiol* 2005;98:319-23.
- ① 49. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock: Should we emergently revascularize occluded coronaries for cardiogenic shock? SHOCK Investigators. *N Engl J Med* 1999;341:625-34.

COMPLICATIONS FOLLOWING PERCUTANEOUS INTERVENTION

Access Complications (3%)

- Hemorrhage, laceration, thrombosis/occlusion, embolism, pseudoaneurysm, arteriovenous fistula, infection; monitor for hematoma and blood flow to limb distal to access site
- Cardiology and/or vascular surgery services should be made aware of suspected access complications
- Hemorrhage is controlled with direct pressure on the arterial puncture site

Contrast Nephropathy (3%-7%)

- Possibly prevented with intravenous saline and/or N-acetylcysteine 600 mg po BID 1 day prior to

procedure¹; risk highest in patients with creatinine greater than 2.0; most effectively prevented by limiting the amount of contrast material

Percutaneous Transluminal Coronary Angioplasty (PTCA) Without Stent²

- 90% success rate in narrowed (not occluded) artery to achieve less than 50% narrowing post-intervention
- Acute complications
 - Abrupt closure by dissection, thrombosis, or vasospasm (2%-8%) within 24 hours of PTCA; only 25% of these complications occur after the patient leaves the catheterization laboratory; management includes aspirin, nitrates, oxygen, and revascularization
 - 3%-7% of patients will need emergent bypass
 - Myocardial infarction occurs in 3%-5%
 - Death occurs in 0%-2%
- Chronic complications: restenosis rate of 35%, and up to 60% when chronic occlusions are dilated; usually will occur within 6 months of PTCA

Stent-Related Complications

Acute

- In-stent thrombosis: hours to days, average of 10 hours postintervention
- Bare metal stents (usually up to 4 weeks): <1% in the context of aspirin and clopidogrel; as high as 3% on aspirin alone³
- Drug-eluting
 - Concern remains that the slowed endothelialization of the newer drug-eluting stents allows a longer period for thrombosis versus bare stents
 - Definitive studies are pending, but it is common to continue clopidogrel and aspirin for at least 6 months postprocedure⁴

Chronic

- In-stent restenosis: smooth muscle proliferation process (1-6 months, rare >12 months)
 - Bare metal stent restenosis: 20% restenosis rate over the life of the stent
 - Drug-eluting stent: data vary and are limited but likely about an 8% restenosis rate



Patient Care Warnings

- Oral clopidogrel plays an important role in the post-intervention period
- Routinely document distal pulses on the same side as the access site

References

1. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: A randomized controlled trial. *JAMA*. 2003;289:553-58.
2. Landau C, Lange RA, Hillis LD, et al. Percutaneous transluminal coronary angioplasty. *N Engl J Med* 1994;330:981-93.
3. Second SYMPHONY Investigators. Randomized trial of aspirin, sibrافiban, or both for secondary prevention after acute coronary syndromes. *Circulation* 2001;103:1727-33.
4. McFadden EP, Stabile E, Regard E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of anti-platelet therapy. *Lancet* 2004;364:1519-21.

INTRA-AORTIC BALLOON PUMPS

Definitions

- The intra-aortic balloon pump (IABP) is a circulatory assist device
- Can be used for the treatment of:
 - Cardiogenic shock and low output states^{1,2}

- Intractable angina that is unresponsive to medical therapy³
- Weaning patients from cardiopulmonary bypass
- Adjunctive therapy after thrombolysis in patients at high risk of reocclusion⁴
- Adjunctive therapy for patients at high risk or with complicated angioplasty⁵
- Prophylaxis in patients with severe left main disease or critical aortic stenosis with upcoming surgery⁶
- Temporary hemodynamic support for acute infarction with significant left ventricular dysfunction^{7,8}
- Acute myocardial infarction (AMI), severe acute mitral regurgitation, and ventricular septal defect^{7,9}
- AMI with hypotension not responsive to other interventions⁷
- Management of medically refractory ventricular arrhythmias in selected patients¹⁰
- Works by displacing blood to the proximal aorta by inflation during diastole; reduces aortic volume and afterload during systole through a vacuum effect created by rapid deflation of the balloon
- The balloon is synchronized to deflate during early systole⁹
 - Decreases left ventricular (LV) afterload, therefore enhancing LV ejection and stroke volume
 - Leads to reduced myocardial oxygen demand¹¹
- The balloon then inflates during early diastole⁹
 - Increases coronary blood flow and peripheral perfusion¹²
 - Augmentation of diastolic arterial pressure¹³
- The effects can be variable based on the volume of the balloon in relation to the diameter of the aorta, its position in the aorta, patient's heart rate and rhythm, and compliance of the aorta¹⁴
- Expected changes in the hemodynamic profile of patients with cardiogenic shock¹
 - Decrease in systolic pressure by approximately 20%

- Increase in diastolic pressure by approximately 30%
- Decrease in heart rate by less than 20%
- Decrease in mean pulmonary capillary wedge pressure by approximately 20%
- Increase in cardiac output by approximately 20%
- Coronary blood flow
 - Some studies show little to no effect^{1,15}
 - Others studies show an increase, occurring when coronary vascular beds are maximally dilated by ischemia, leading to pressure-dependant autoregulation and flow (unless there is a severe vessel stenosis)^{1,12}
- May reduce periprocedural and postprocedural complications in patients with AMI when used prophylactically in patients with poor LV function¹⁶
- Some beneficial results noted when adjunctive IABP was used following percutaneous transluminal coronary angioplasty (PTCA) in patients with AMI¹⁷
- Currently, IABP is used for high-risk PTCA, but not usually with primary angioplasty of AMI or after failed thrombolytics, unless cardiogenic shock develops

Placement^{11,18}

- Inserted percutaneously, with a sheath in the common femoral artery, with a sized (8 or 9.5 Fr) catheter
- IAPB tip should be positioned in the descending aorta, distal to the left subclavian artery, and proximal to the renal arteries
- IAPB is connected to a drive console with a gas reservoir (helium or carbon dioxide), a monitor for electrocardiogram (ECG) and pressure-wave recordings, adjustments for inflation/deflation timing, triggering selection, and a back-up power source

Settings⁹

- Inflation and deflation are synchronized to the patient's cardiac cycle using ECG signal, arterial wave, or an intrinsic pump rate
- Inflation should occur at the beginning of diastole, seen as the dicrotic notch on the arterial waveform; deflation should occur immediately prior to the arterial upstroke
- Inflation starts in middle of T wave, and deflation starts prior to the ending QRS complex
- Initially set at a rate of 1:1 or 1:2
- Patient is usually weaned from the pump at rates of 1:2, 1:3, and 1:4 over several hours

Contraindications⁹

- Significant aortic valve (AV) insufficiency or severe AV shunting
- Tortuous or aneurysmal descending thoracic or abdominal aorta
- Aortic dissection
- Uncontrolled sepsis
- Uncontrolled bleeding or inability to anticoagulate patient
- Severe bilateral peripheral vascular disease, with or without bilateral femoral-popliteal bypass grafts

Guide to Management

Following Placement⁹

- Chest x-ray to identify location of the IABP tip marker
- Anticoagulation: heparin to maintain appropriate activated partial prothrombin time (aPPT) levels

Complications

- Vascular^{18,19}:
 - Limb ischemia: iatrogenic occlusion of subclavian

or femoral arteries (look for decreases in pulses of related limb, abnormal sensation, color or temperature)

- Renal ischemia: follow serum creatinine and urine output
- Severe bleeding, hemorrhage, and hematoma
- Vascular laceration requiring surgical repair
- Arterial dissection
- Femoral artery thrombosis
- Nonvascular²⁰:
 - Balloon leak or rupture
 - Cholesterol or gas embolization
 - Infection and sepsis
 - Cerebral vascular accident
- Clinical factors that increase complications^{8,21}:
 - Older age
 - Female gender
 - Small body surface area
 - Diabetes mellitus
 - Peripheral vascular disease
 - Hypertension
 - Prolonged support
 - Larger catheter size



Patient Care Warnings

- Check postplacement chest x-ray and monitor limb pulses, chest imaging, and serum creatinine/urine output to assess for vessel occlusion and migration of IABP
- Requires anticoagulation and strict monitoring of aPTT levels
- Verify timing of inflation and deflation by noting arterial waveform characteristics

References

- ② 1. Scheidt, S, Wilner, G, Mueller, H, et al. Intraaortic balloon counterpulsation in cardiogenic shock. *N Engl J Med* 1973; 288:979.
- ② 2. Anderson RD, Ohman EM, Holmes, DR, et al. Use of intraaortic balloon counterpulsation in patients presenting with cardiogenic shock: Observations from the GUSTO-1 study. *J Am Coll Cardiol* 1997;30:708.
- ③ 3. Weintraub RM, Voukydis PC, Aroesty JM. Treatment of preinfarction angina with intraaortic balloon counterpulsation and surgery. *Am J Cardiol* 1974;34:809.
- ① 4. Ohman EM, Califf RM, George BS, et al. Use of intraaortic balloon pumping as adjunct to reperfusion therapy in acute myocardial infarction. The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Trial Study Group. *Am Heart J* 1991;121:895.
- ③ 5. Lincoff AM, Popma SJ, Ellis SG, et al. Percutaneous support devices for high risk or complicated angioplasty. *J Am Coll Cardiol* 1991;17:770.
- ③ 6. Rajai HR, Hartman CW, Innes BJ, et al. Prophylactic use of intraaortic balloon pump in aortocoronary bypass for patients with left main coronary artery disease. *Ann Surg* 1978;187:118.
- ③ 7. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines on Management of Acute Myocardial Infarction). *Circulation* 2004;110:588.
- ② 8. Ferguson JJ, Cohen M, Freedman RJ, et al. The current practice of intra-aortic balloon counterpulsation: Results from the Benchmark registry. *J Am Coll Cardiol* 2001;38:1456.
- ③ 9. Peterson JC, Deborah JC. Systematic review: Intra-aortic balloon counterpulsation pump therapy: A critical appraisal of the evidence for patients with acute myocardial infarction. *Crit Care* 1998;2:3.
- ② 10. Fotopoulos GD, Mason MJ, Walker S, et al. Stabilisation of medically refractory ventricular arrhythmia by intra-aortic balloon counterpulsation. *Heart* 1999;82:96.
- ③ 11. Williams DO, Korz KS, Gewirtz H, et al. The effect of intraaortic balloon counterpulsation on regional myocardial blood flow and oxygen consumption in the presence of coronary artery stenosis in patients with unstable angina. *Circulation* 1982;66:593.
- ③ 12. Kern MJ, Aguirre FV, Bach R, et al. Augmentation of coronary blood flow by intraaortic balloon pumping in patients after coronary angioplasty. *Circulation* 1993;87:500.
- ③ 13. Gurbel PA, Anderson D, MacCord CS. Arterial diastolic pressure augmentation by intraaortic counterpulsation enhances

the onset of coronary reperfusion by thrombolytic therapy. *Circulation* 1994;89:361-65.

- ③ 14. Weber KT, Janicki JS. Intraaortic balloon counterpulsation: A review of physiological principles, clinical results, and device safety. *Ann Thorac Surg* 1974;17:602.
- ② 15. Port SC, Patel S, Schmidt DH. Effects of intraaortic balloon counterpulsation on myocardial blood flow in patients with severe coronary artery disease. *J Am Coll Cardiol* 1984;3:367.
- ② 16. Brodie BR, Stuckey TD, Hansen C, et al. Intra-aortic balloon counterpulsation before primary percutaneous transluminal coronary angioplasty reduces catheterization laboratory events in high-risk patients with an acute myocardial infarction. *Am J Cardiol* 1999;84:18.
- ① 17. Stone GW, Marsalese D, Brodie BR, et al. A prospective, randomized evaluation of prophylactic intraaortic balloon counterpulsation in high risk patients with acute myocardial infarction treated with primary angioplasty. Second Primary Angioplasty in Myocardial Infarction (PAMI-II) Trial Investigators. *J Am Coll Cardiol* 1997;29:1459.
- ② 18. Barnett MG, Swartz MT, Peterson GJ, et al. Vascular complications from intraaortic balloons: risk analysis. *J Vasc Surg* 1994;19:81.
- ② 19. Patel JJ, Kopisyansky C, Boston B, et al. Prospective evaluation of complications with percutaneous intraaortic balloon counterpulsation. *Am J Cardiol* 1995;76:1205.
- ③ 20. Aru GM, King Jr JU, Hovaguimian H, et al. The entrapped balloon: Report of a possibly serious complication. *J Thorac Cardiovasc Surg* 1986;91:146.
- ② 21. Gottlieb SO, Brinker JA, Borkon AM, et al. Identification of patients at high risk for complications of intraaortic balloon counterpulsation: A multivariate risk factor analysis. *Am J Cardiol* 1984;53:1135.

CONGESTIVE HEART FAILURE AND SYSTOLIC DYSFUNCTION

Definition, Etiology, and Epidemiology

- Results from any structural or functional cardiac disorder that impairs ventricular ejection of blood
- Systolic dysfunction implies impaired cardiac contractility
- Approximately 5 million people in the United States alone with congestive heart failure (CHF), nearly

400,000 new cases annually, and over 200,000 deaths attributable to a diagnosis of heart failure each year¹

- Despite improvements in diagnosis and treatment, 5-year survival is about 50%
- Most common causes of systolic dysfunction are ischemic heart disease, idiopathic dilated cardiomyopathy, hypertension, and valvular heart disease
- Other causes include myocarditis, infiltrative diseases, substance abuse, connective tissue diseases, peripartum cardiomyopathy, nutritional deficiencies (e.g. thiamine, selenium), prolonged tachyarrhythmias, and familial disorders

Pearls of the History and Physical Examination

History

- Assess for symptoms due to excess fluid accumulation
 - Peripheral edema, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, weight gain, abdominal distention, nausea (due to bowel wall edema), right upper quadrant pain (due to hepatic congestion and capsule distention)
- Assess for symptoms due to poor cardiac output
 - Fatigue, generalized weakness, lightheadedness, near-syncope, syncope, anorexia
- Ask about hypertension, diabetes, dyslipidemia, coronary artery disease (i.e. angina, myocardial infarction), history of rheumatic fever, exposure to cardiotoxic agents, intravenous (IV) drug abuse, cocaine use, alcohol use, travel history, infectious disease history
 - Take detailed family history of heart failure, coronary artery disease (CAD), and sudden cardiac death
- Determine New York Heart Association (NYHA) classification

- Class I: symptoms with extreme exertion
- Class II: symptoms with normal levels of exertion
- Class III: symptoms with less than normal levels of exertion
- Class IV: symptoms at rest

Physical Examination

- Evaluate for evidence of volume overload
 - Pulmonary congestion: rales (may be absent in patients with chronic disease even in the presence of elevated wedge pressures), pleural effusions
 - Peripheral edema: pitting lower extremity edema, ascites, hepatosplenomegaly, presacral edema, scrotal edema
 - Jugular venous distention (JVD): >10 cm H_2O indicates elevated circulating volume; in upright position (90 degrees), internal jugular venous pulsations above the level of the clavicle correlate with the presence of JVD
 - An abnormal hepatojugular reflux in the absence of JVD can also suggest elevated circulating blood volume
 - Valsalva maneuver: systolic blood pressure (SBP) is calculated in the supine position, and cuff pressure is increased to 15 mm Hg above the systolic pressure; patient performs Valsalva maneuver after normal respiratory cycle for 10 seconds and then resumes normal respiration
 - Normal LV function: Korotkoff's sound appears initially on Valsalva maneuver, then disappears within a few seconds, but returns 3-10 seconds after resumption of normal respiration
 - Impaired left ventricle (LV) function: Korotkoff's sound fails to reappear with normal respiration
 - Severely impaired LV function: Korotkoff's sound heard throughout Valsalva maneuver, disappears on relaxation
- Evaluate for evidence of impaired cardiac output

- Cool extremities: peripheral vasoconstriction
- Pulsus alternans: virtually pathognomonic of severe LV dysfunction; alternating strong with weak pulses
- Palpable dirotic notch: represents closure of the aortic valve; severe LV dysfunction results in accentuation of closure pulsation due to compensatory increase in systemic vascular resistance (SVR)
- Proportional pulse pressure ($[\text{SBP} - \text{diastolic blood pressure (DBP)}]/\text{SBP}$) $< 25\%$ suggests cardiac index of $< 2.2 \text{ L/min/m}^2$
- Evaluate for palpable or audible S_3 gallop
- Evaluate for Cheyne-Stokes respirations (poor LV function and decompensated CHF)

Diagnostic Studies and Laboratory Values

Blood Tests

- Serum tests: complete blood count (CBC) (exclude anemia), electrolytes (blood urea nitrogen, creatinine, hyponatremia, prerenal azotemia), liver function tests (may be elevated due to hepatic congestion), urinalysis, thyroid function tests (hyper- and hypothyroidism can present as heart failure)
- Plasma B-type natriuretic peptide (BNP): useful for rapidly differentiating dyspnea due to cardiac dysfunction from pulmonary or other causes; BNP $< 100 \text{ pg/mL}$ has high negative predictive value for LV dysfunction^{2,3}

Other Diagnostic Tests

- Electrocardiogram (ECG): recommended for all patients with suspected heart failure⁴; used initially to determine if acute myocardial injury/infarction or arrhythmia is present
 - Normal ECG is highly unusual in patient with impaired LV function⁵⁻¹⁰

- Presence of pathological Q waves does not correlate with LV function¹¹
- Chest x-ray: recommended for all patients with suspected heart failure
 - Cardiomegaly is only consistent radiographic finding seen in patients with end-stage CHF,^{12,13} but is poor predictor of LV function¹⁴
 - Evidence of elevated circulating blood volume: pulmonary vascular redistribution, interstitial edema,¹⁵ perivascular or peribronchial cuffing, hilar haze, alveolar filling pattern of pulmonary edema
 - Chest x-ray can be normal even with high-wedge pressures in patients with advanced heart failure due to augmented lymphatic drainage¹⁶
- Echocardiogram: recommended for all patients with suspected heart failure; sensitivity and specificity for diagnosis of heart failure as high as 80%-100%¹⁷
 - Systolic dysfunction defined as LV ejection fraction (LVEF) $\leq 40\%$

Guide to Management

Risk Stratification and Assessment of Hemodynamic Profile

	No Congestion	Congestion
Adequate Perfusion	Warm and dry	Warm and wet
Low Perfusion	Cold and dry	Cold and wet

Low perfusion: narrow pulse pressure, cool forearms/legs, lethargy, hypotension, hyponatremia, azotemia; Congestion: orthopnea, JVD, edema, ascites, rales, S3 (Adapted from Reference 18)

Acute Management of the “Warm and Wet” Patient

- Diuretics: produce rapid symptomatic improvement in pulmonary and peripheral edema
 - IV loop diuretics (furosemide < bumetadine < torsemide) to overcome impaired absorption of oral agents in setting of bowel edema

- Goal of therapy is weight reduction of 0.5-1.0 kg/d
- May use bolus therapy or continuous infusion
- Overcome resistance by continuous infusion of diuretic or use of additional diuretic (i.e., metolazone)
- Monitor for potassium and magnesium depletion with therapy
- Unknown effects on morbidity and mortality rates due to lack of long-term trials

Acute Management of the “Cold and Wet” Patient

- Transfer patient to intensive care unit (ICU)
- Reduce beta blockers and angiotensin-converting enzyme (ACE) inhibitors until stabilization is achieved
- Diuretics as bolus therapy or continuous infusion
- IV vasodilators
 - Nitroglycerin: lowers filling pressures through venous and arterial vasodilation, thereby increasing cardiac output and aiding diuresis¹⁹
 - Use only in patients with reserve contractility (SBP>100) who can still augment their ejection fraction; otherwise, will result in hypotension/shock
 - Start with low dose (e.g., <5 µg/kg/min) with goal to reduce mean arterial pressure (MAP) by 10%-25%; higher doses result in increased angiotensin II, aldosterone, and reflex tachycardia
 - Tolerance is common
 - Nitroprusside: decreases afterload and thus increases cardiac output indirectly
 - Should be used only in patients with presumably elevated SVR and reserve contractility (SBP>100)
 - Ideally, should use with pulmonary artery (PA) catheter due to unpredictable effects of this medication on SVR
 - Tailored therapy: goal to use nitroprusside + diuretics +/- hydralazine/nitrates to decrease SVR (<1200) and wedge pressure (<16), increase cardiac index (>2.2)

while slowly adding ACE inhibitor or angiotensin II receptor blocker (ARB); PA catheter-guided therapy resulted in no improvement in mortality or hospitalization rates, but trend for greater functional improvement in class IV patients with CHF²⁰

- Cyanide toxicity limits prolonged use; should not be used in patients with creatinine >2.5 mg/dL
- Start at dose of 0.5 µg/kg/min, with goal in range of 1-2 µg/kg/min (maximum level of 5 µg/kg/min to avoid toxicity)
- Inotropic agents
 - Increased mortality rate seen in several trials^{21,22}
 - Should be used in patients with shock, for palliation in end-stage CHF, and as bridge to transplantation
 - Goal is to keep exposure to inotropic agents to a minimum and initiate at the lowest possible dose
 - Dobutamine
- Nesiritide: unique vasodilator identical to circulating BNP
 - Results in natriuresis, diuresis (without kaliuresis)¹⁹
 - Increases cardiac output and coronary blood flow; causes venodilation; decreases AII, aldosterone, and renin secretion; does not increase inotropy
 - Should be avoided in patients with low filling pressures, as it can result in hypotension/shock
 - 2 µg/kg bolus, followed by 0.01 µg/kg/min infusion, can be increased at ≥3h intervals (1 µg/kg bolus followed by an increase of 0.005 µg/kg/min) to a maximum of 0.03 µg/kg/min¹⁹
 - Continuous infusion at a rate of 5-7.5 µg/kg/min
 - Monitor for tachyarrhythmias
 - Patients should have hemodynamic monitoring for at least 48 hours following infusion
 - Use in patients not already on chronic beta blocker therapy
 - Milrinone

- Phosphodiesterase inhibitor that functions as both inotropic agent and vasodilator
- Results in more hypotension than does dobutamine
- Atrial arrhythmias are common
- Use infusion of 0.1-0.2 $\mu\text{g/kg/min}$
- Dopamine
- Nesiritide: unique vasodilator identical to circulating BNP
 - Thought to result in natriuresis, diuresis (without kaliuresis)
 - Increases cardiac output and coronary blood flow; causes venodilation; decreases AII, aldosterone, and renin secretion; does not increase inotropy
 - Should be avoided in patients with low filling pressures, as it can result in hypotension/shock
 - 2 $\mu\text{g/kg}$ bolus, followed by 0.01 $\mu\text{g/kg/min}$ infusion; can be increased at $\geq 3\text{h}$ intervals (1 $\mu\text{g/kg}$ bolus followed by an increase of 0.005 $\mu\text{g/kg/min}$) to a maximum of 0.03 $\mu\text{g/kg/min}$
 - Long-term outcome studies are still pending

Chronic Management

- ACE inhibitors: improve survival,²³⁻²⁶ reduce after-load, and modify pathological cardiac remodeling
 - Begin therapy with low doses (enalapril 2.5 mg BID or captopril 6.25 mg TID) to reduce likelihood of hypotension or azotemia
 - Titrate dose to goal (i.e., enalapril 10 mg BID, captopril 50 mg TID, lisinopril 40 mg daily); once at goal, should titrate further only as needed for BP control
 - Monitor for hypotension, hyperkalemia, renal insufficiency, cough, and/or angioedema
- ARBs should be used in patients with class II or III heart failure who cannot tolerate ACE inhibitors²⁷
- Hydralazine and nitrates: produce modest benefits in a general population with heart failure but are

less effective than ACE inhibitors; result in afterload reduction to improve cardiac output and aid diuresis

- Start hydralazine at 25 mg TID (titrated up to 100 mg TID) and isosorbide dinitrate at 10 mg TID (titrated up to 40 mg TID)
- Indicated for patients with heart failure who cannot tolerate ACE inhibitor or ARB
- For black patients, isosorbide dinitrate (120 mg daily divided TID) and hydralazine (225 mg daily divided TID) in addition to standard therapy for heart failure (including neurohormonal blockade) increased survival in advanced heart failure (NYHA III-IV)²⁸
- Digoxin: results in reduction of symptoms and hospitalization, with no mortality benefit²⁹
 - Goal serum concentration of 0.5-0.8 ng/mL based upon subgroup analyses of DIG trial
 - Should be used in patients who remain symptomatic despite ACE inhibitor, beta blocker, and diuretic therapy; initiated as an outpatient (not useful in patients with acute decompensated heart failure)
- Aldosterone antagonists
 - Spironolactone (25-50 mg/d) resulted in improved mortality rate in patients with NYHA class III and IV heart failure based on RALES trial³⁰
 - Eplerenone was associated with a 15% reduction in overall mortality rate in patients with recent myocardial infarction and LV dysfunction with symptomatic heart failure (EPHESUS)³¹
- Beta blockers: act principally by inhibiting adverse effects of sympathetic nervous system in patients with heart failure; no role in the decompensated heart failure patient and, therefore, should be initiated only in the patient with stable, well-compensated CHF



Patient Care Warnings

- ICU care is recommended for any patient with hemodynamic instability or evidence of poor perfusion
- Monitor electrolytes closely during diuresis to avoid hypokalemia and hypomagnesemia
- Never initiate beta blocker therapy in patients with evidence of decompensation as this will only exacerbate the decompensated state
- Avoid milrinone in patients with hypotension
- Drugs to avoid in patients with heart failure include nonsteroidal anti-inflammatory drugs (NSAIDs), which may increase afterload and blunt the renal effects of diuretics; metformin due to the increased risk of lactic acidosis; most antiarrhythmic agents, which have negative inotropic activity; and thiazolidinediones, which appear to result in fluid retention

References

- ③ 1. O'Connell JB, Bristom MR. Economic impact of heart failure in the United States: Time for a different approach. *J Heart Lung Transplant* 1994;13:107-12.
- ① 2. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;247:161.
- ① 3. McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in the emergency diagnosis of heart failure: Analysis from Breathing Not Properly (BNP) multinational study. *Circulation* 2002;106:416.
- ③ 4. Committee on Evaluation and Management of Heart Failure. Guidelines for the evaluation and management of heart failure: Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 1995;26:1376-98.
- ② 5. Davie AP, Francis CM, Love MP, et al. Value of the electrocar-

- diogram in identifying heart failure due to left ventricular systolic dysfunction. *Br Med J* 1996;312:222.
- ② 6. Gillespie ND, McNeill G, Pringle T, et al. Cross sectional study of contribution of clinical assessment and simple cardiac investigations to diagnose left ventricular systolic dysfunction in patients admitted with acute dyspnoea. *Br Med J* 1997;314:936-40.
 - ③ 7. Cleland JGF, Habib F. Assessment and diagnosis of heart failure. *J Intern Med* 1996;239:317-25.
 - ③ 8. The Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741-51.
 - ② 9. Christian TF, Miller TD, Chareonthaitawee P, et al. Prevalence of normal resting left ventricular function with normal rest electrocardiograms. *Am J Cardiol* 1997;79:1295-98.
 - ② 10. O'Keefe JH, Zinsmeister AR, Gibbons RJ. Value of normal electrocardiographic findings in predicting left ventricular function in patients with chest pain and suspected coronary artery disease. *Am J Med* 1989;86:658-62.
 - ② 11. Askenazi J, Parisi AF, Cohn PF, et al. Value of the QRS complex in assessing left ventricular ejection fraction. *Am J Cardiol* 1978;41:494-99.
 - ② 12. Mahdyoon H, Klein R, Eyler W, et al. Radiographic pulmonary congestion in end-stage congestive heart failure. *Am J Cardiol* 1989;63:625-27.
 - ③ 13. Harlan WR, Oberman A, Grimm R, et al. Chronic congestive heart failure in coronary artery disease: Clinical criteria. *Ann Intern Med* 1977;86:133-38.
 - ② 14. Madsen EB, Gilpin E, Slutsky RA, et al. Usefulness of the chest x-ray for predicting abnormal left ventricular function after acute myocardial infarction. *Am Heart J* 1984;108:1431-36.
 - ② 15. Badgett RG, Mulrow CD, Otto PM, et al. How well can the chest radiograph diagnose left ventricular dysfunction? *J Gen Intern Med* 1996;11:625-34.
 - ② 16. Chakko S, Woska D, Martinez H, et al. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: Conflicting results may lead to inappropriate care. *Am J Med* 1991;90:353-59.
 - ② 17. Erbel R, Schweizer P, Krebs W, et al. Sensitivity and specificity of two-dimensional echocardiography in detection of impaired left ventricular function. *Eur Heart J* 1984;5:477
 - ③ 18. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *JAMA* 2002;287:628-40.
 - ① 19. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs. nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial. *JAMA* 2002;387:1531-40.

- 1 20. Shah MR, O'Connor CM, Sopko G, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness (ESCAPE): Design and rationale. *Am Heart J* 2001;141:528-35.
- 1 21. Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): A randomized double-blind trial. *Lancet* 2002;360:196-202.
- 1 22. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: A randomized controlled trial. Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. *JAMA* 2002;287:1541-47.
- 1 23. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med* 1992;327:685.
- 1 24. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303.
- 1 25. Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429.
- 1 26. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325:293.
- 1 27. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The CHARM-Alternative trial. *Lancet* 2003;362:772.
- 1 28. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351:2049-57.
- 1 29. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525.
- 1 30. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709.
- 1 31. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309.

DIASTOLIC DYSFUNCTION, RESTRICTIVE CARDIOMYOPATHY, CONSTRICTIVE PERICARDITIS, AND HYPERTROPHIC CARDIOMYOPATHY

Definition, Etiology, and Epidemiology

- Hypertrophic cardiomyopathy (HCM): autosomal-dominant inheritance resulting in left ventricular (LV) hypertrophy; may see any pattern of diffuse or segmental LV thickening
 - Mutations can be present in any one of 10 genes, each encoding protein components of the cardiac sarcomere with either contractile, structural, or regulatory functions
 - Three of the HCM-causing mutant genes (more than half of genotyped patients to date) predominate in frequency: beta-myosin heavy chain, myosin-binding protein C, and cardiac troponin-T
 - Prevalence: 1 in 500 people, males and females equally affected
 - Mutations in myosin-binding protein C gene have demonstrated age-related penetrance as well as late onset of the phenotype in which delayed and de novo appearance of LVH on echocardiogram occurs in midlife and later¹
- Restrictive cardiomyopathy (RCM): myocardial disease that results in impaired ventricular filling, with normal or decreased diastolic volume of either or both ventricles; systolic function usually remains normal, early in the disease, and wall thickness may be normal or increased, depending on the underlying cause
 - Condition usually results from increased stiffness of the myocardium, which causes pressure within the ventricle (or ventricles) to rise precipitously with only small increases in volume²

- These are rare diseases outside the tropics, with cardiac amyloidosis being the most frequently occurring in Western societies

CLASSIFICATION OF TYPES OF RCM ACCORDING TO CAUSE²

Type	Cause
Myocardial	
Noninfiltrative	Idiopathic cardiomyopathy, familial cardiomyopathy, hypertrophic cardiomyopathy, scleroderma, pseudoxanthoma elasticum, diabetic cardiomyopathy
Infiltrative	Amyloidosis, sarcoidosis, Gaucher's disease, Hurler's disease, fatty infiltration
Storage diseases	Hemochromatosis, Fabry's disease, glycogen storage diseases
Endomyocardial	Endomyocardial fibrosis, hypereosinophilic syndrome, carcinoid heart disease, metastatic cancer, radiation, toxic effects of anthracycline, drugs causing fibrous endocarditis (serotonin, methysergide, ergotamine, mercurial agents, busulfan)

- Constrictive pericarditis (CP): chronic, fibrous, or callous thickening of the wall of the pericardial sac that is so contracted that the normal diastolic filling of the heart is impaired

ETIOLOGIES OF CP AND FREQUENCY OF OCCURRENCE³

Cause	Percentage
Idiopathic	45%
Post-coronary artery bypass grafting	30%
Tuberculosis	10%
Radiation-induced	5%
Collagen vascular disease	5%
Others (malignancy, uremia, purulent)	5%

- Heart failure with preserved systolic function or diastolic dysfunction (DD)⁴
 - Occurrence of clinical signs and symptoms of heart failure with normal ejection fraction
 - Due to increased LV mass and cardiac fibrosis resulting in reduced compliance and chamber size
 - Congestive symptoms appear when the heart is unable to adequately fill in diastole
 - Risk factors: increased age (>65 years), female gender, and history of chronic systemic hypertension
 - Prevalence of condition in elderly patients with clinical heart failure is $\geq 50\%$ ⁵
 - Patients often present with the acute onset of symptoms and abrupt clinical deterioration; commonly known as “flash pulmonary edema”

Pearls of the History and Physical Examination

History

- Exercise intolerance, which can be accompanied by orthopnea and paroxysmal nocturnal dyspnea
- Family history, especially in HCM; individuals often have a family history of sudden death in young relatives
- HCM patients frequently complain of progressive symptoms, including exertional dyspnea, chest pain (either typical of angina or atypical in nature), and impaired consciousness, including syncope, near-syncope, or presyncope (i.e., dizziness/lightheadedness); however, patients may have no complaints prior to an episode of sudden cardiac death (SCD)
- DD patients frequently do not complain of edema, whereas individuals with RCM/CP frequently have edema; this results from impaired RV filling in RCM/CP
- Obtain history of other comorbid conditions (renal failure, malignancy, hypertension, etc.)

- Obtain exposure history (risk factors for tuberculosis, prior chest radiation, recent bypass surgery)

Physical Examination

- Jugular venous distention (JVD): present in CP and RCM; not typically present in DD
 - Kussmaul's sign: rise in JVP (as opposed to normal fall) with inspiration; usually present in CP and occasionally present in RCM
- Peripheral edema or ascites: present in CP and RCM; not typically present in DD
- Pulmonary congestion: rales often present in all conditions (may be absent in patients with chronic disease), pleural effusions (dullness to percussion and bronchial or absent breath sounds in lung bases)
- Cardiac
 - HCM: loud, harsh, midsystolic murmur often present at left lower sternal border; murmur increases in intensity with handgrip and Valsalva maneuver; murmur decreases in intensity on leg raise or squatting
 - S_3 more common in RCM (can also hear S_4)
 - S_4 usually present in DD
 - Apical impulse present in RCM, usually absent in CP
 - Regurgitant murmurs often present in RCM, usually absent in CP
 - Pericardial "knock" corresponding to the early, abrupt cessation of ventricular filling is a characteristic finding of CP; heard early in diastole³

Diagnostic Studies and Laboratory Values

Chest Radiograph

- Pericardial calcifications point toward diagnosis of CP
- Radiographic features of CHF are usually present (central pulmonary vascular congestion, cephaliza-

tion, with Kerley B lines and pleural effusions in severe cases)

- Unlike dilated cardiomyopathy, cardiomegaly is not present in diastolic heart failure

Electrocardiogram (ECG)

- Low voltage present in most cases of RCM, particularly amyloidosis, and less than 50% of CP cases
- Conduction abnormalities often present in RCM, particularly amyloid; LVH often present in DD and HCM

Echocardiogram (Critical to Diagnosis)

- HCM
 - LVH nearly always present, usually with asymmetric septal hypertrophy (ASH)
 - Dynamic left ventricular outflow tract (LVOT) obstruction occurs as a result of systolic anterior motion of the mitral valve leaflets and midsystolic contact with the hypertrophied septum
 - LVOT gradient is an important prognostic indicator: those with gradients >30 mm Hg have a twofold increased risk of SCD, and more than fourfold increased risk of stroke and heart failure
- RCM
 - Increased wall thickness with granular sparkling (“starry sky”) texture; valvular regurgitation present
 - Doppler shows increased early diastolic filling velocity (mitral E velocity), decreased atrial filling velocity (mitral A velocity), and increased ratio of early diastolic filling to atrial filling
- CP
 - Abrupt displacement of the interventricular septum during early diastole (septal bounce) may be observed; may see pericardial thickening
 - Signs of systemic venous congestion, such as dilation of hepatic veins and distention of the inferior vena cava (IVC) with blunted respiratory fluctua-

tion (IVC plethora), are almost always seen, but are nonspecific

- Doppler findings: inspiratory decrease in LV filling and limitation of RV filling on expiration; typically, patients with CP demonstrate $\geq 25\%$ increase in mitral E velocity during expiration compared with inspiratory phase; mitral E deceleration time is usually but not always < 160 msec; these Doppler echocardiographic findings have an 88% sensitivity for the diagnosis of CP³
- DD
 - Concentric LVH
 - Mitral inflow pattern consistent with impaired relaxation
 - Absence of valvular abnormalities (particularly aortic stenosis)
 - Preserved or increased ejection fraction

Cardiac Catheterization

- Used to define hemodynamic abnormalities, particularly if CP or RCM is considered
- RCM
 - Typically atrial, RV diastolic, pulmonary capillary wedge, and LV diastolic pressures are equal and elevated
 - Right atrial pressure demonstrates a preserved x -descent with a prominent early y -descent and roughly equal a and v wave heights, with the resultant “M” or “W” shape evident in the jugular vein pressure tracings
 - Intraventricular pressure recordings reveal an early, marked diastolic dip followed by a plateau (dip and plateau or square root sign), corresponding to the early and rapid ventricular filling pattern

Computed Tomography or Magnetic Resonance Imaging

- May show a thickened pericardium in CP

Endomyocardial Biopsy

- Necessary for diagnosis and for determining etiology of RCM if it is suspected

Guide to Acute Management

Hypertrophic Cardiomyopathy

- Beta blockers are preferred for symptomatic patients with outflow gradients present only on exertion¹
- High risk for development of atrial fibrillation (see section titled Atrial Fibrillation and Flutter)
 - May consider direct current cardioversion (DCCV) over medical therapy earlier in disease process
- SCD risk stratification determined by following associations:
 - Prior cardiac arrest or spontaneously occurring and sustained VT
 - Family history of a premature HCM-related SCD, particularly if sudden, in a close relative, or if multiple in occurrence
 - Identification of a high-risk mutant gene
 - Unexplained syncope, particularly in young patients or when exertional and/or recurrent
 - Nonsustained VT (of 3 beats or more and of at least 120 beats/min) evident on ambulatory (Holter) ECG recordings
 - Abnormal blood pressure (BP) response during upright exercise that is attenuated or hypotensive; this is indicative of hemodynamic instability and of greater predictive value in patients younger than 50 years
 - Extreme LVH with maximum wall thickness ≥ 30 mm, particularly in adolescents and young adults
 - Decision to place implantable cardiac defibrillator (ICD) for primary prevention of SCD is based upon the presence of above-risk factors, age of

patient, and preferences of physician and patient¹

- Surgical myomectomy and alcohol septal ablation are reserved for patients with obstructive symptoms refractory to medical therapy, resting or exertional gradients >50 mm Hg, and New York Heart Association class III or IV CHF

Restrictive Cardiomyopathy

- Diuretics
 - Use gently for relief of symptoms as aggressive diuresis is not well tolerated
- Patients depend upon atrial contribution to ventricular filling; development of atrial fibrillation is, therefore, not well tolerated and the development of a rapid ventricular response, which further compromises ventricular filling, may cause circulatory collapse
 - Digoxin should be avoided if amyloidosis is suspected
 - Patients with atrial fibrillation and rapid ventricular response should be monitored in an intensive care unit as rate control can be difficult, with both tachycardia and bradycardia being extremely dangerous
- Prognosis depends upon etiology of RCM; amyloidosis is associated with dismal prognosis, with an average survival of 2 years from diagnosis

Constrictive Pericarditis

- Use diuretics gently for relief of symptoms
- Diagnosis is essential as pericardiectomy is curative (but high-risk) in this condition; attempt to elucidate etiology if possible

Diastolic Dysfunction

- Flash pulmonary edema: markedly elevated BP and

resultant transient myocardial ischemia are believed to be the cause

- Goal of therapy is pulmonary venodilation to aid in relief of congestive symptoms, rapid control of BP, rapid diuresis, and maintenance of oxygen saturation
- Mechanical ventilation may be necessary for declining patient respiratory effort
- Treatment
 - Oxygen by face mask to maintain oxygen saturation; should patient respiratory effort decline, consider noninvasive ventilation, but prepare patient for emergent endotracheal intubation
 - Intravenous nitroglycerine drip (initial dose 5 µg/min) with rapid titration (every 3-5 minutes)
 - Furosemide 100-120 mg intravenous once
- Inpatient management of DD depends on appropriate diagnosis by echocardiogram
 - Diuresis with furosemide is beneficial for congestive symptoms
 - Patients have a much lower volume reservoir and will require much less diuresis than will patients with systolic dysfunction
 - No treatment guidelines exist for long-term management; consider a cardioselective beta blocker early in the hospital course to aid in diastolic filling
 - Currently limited data to support use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in diastolic heart failure as a means to reduce fibrosis and neurohormonal activation that contribute to the progression of this condition
- Prognosis: mortality approaches two times age-matched controls, with significant morbidity rate (chronic exercise intolerance, frequent exacerbations and hospital admissions, and decreased quality of life)



Patient Care Warnings

- DD may be clinically indistinguishable from systolic heart failure; pay attention to detail in the history and physical examination, which may describe the presence of DD; if there is doubt as to etiology of heart failure, stabilize patient and obtain echocardiogram as soon as possible
- Use care in the diuresis of patients with CP or RCM; patients often become hypotensive with large doses of furosemide, despite the presence of what appears to be an adequate volume reservoir for diuresis (pedal edema, JVD, etc.); excessive diuretic use in patients with RCM may reduce ventricular filling pressures, leading to decreased cardiac output and symptoms of fatigue and lightheadedness, with signs of hypotension and hypoperfusion
- Use digoxin with caution because it is potentially arrhythmogenic, particularly in patients with amyloidosis

References

- ③ 1. Maron BJ, McKenna WJ, Danielson GK. ACC/ESC clinical expert consensus document on hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003;42:1687-713.
- ③ 2. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. *New Engl J Med* 1997;336:267-76.
- ③ 3. Kabbani SS, LeWiner MM. Diastolic function and dysfunction. *Cardiol Clin* 2000;18:501-19.
- ③ 4. Kitzman DW. Heart failure with normal systolic function. *Clin Geriatr Med* 2000;16:489-512.
- ③ 5. Kitzman DW, Gardin JM, Arnold AM, et al: Heart failure with preserved systolic LV function in the elderly: Clinical and echocardiographic correlates from the Cardiovascular Health Study [abstract]. *Circulation* 1996;94:433.

AORTIC DISSECTION

Definition, Etiology, and Epidemiology

- Acute: symptoms present for less than 2 weeks prior to presentation
- Two classification systems
 - DeBakey
 - Type I: involves both ascending and descending aorta
 - Type II: involves ascending aorta only
 - Type III: involves descending aorta only
 - Stanford
 - Type A: any involvement of ascending aorta
 - Type B: involvement limited to descending aorta
- Blood enters the aortic wall via an intimal tear, thereby creating a false lumen in the media

EPIDEMIOLOGY AND RISK FACTORS (INTERNATIONAL REGISTRY OF AORTIC DISSECTION [IRAD])

Epidemiology	Risk Factors
• Incidence in U.S. is 2-4 cases per 100,000 per year¹ • 2000 cases/year in the U.S.² • Peak age of incidence, 40-70 years³ • Males outnumber females 2-3:1⁴ • 38% acute cases are initially missed, and 28% are diagnosed only at autopsy⁴ • In type A dissections, there is a 1% increase in mortality rate for each hour delayed to therapy up to a 50% rate after 48 hours⁴	• Chronic hypertension: estimated to be present in 62%-78% cases⁴ • Abnormalities of collagen: Marfan's syndrome or Ehlers-Danlos syndrome • Age (peak incidence between 40-70 years) • Gender (males outnumber females by approximately 3:1) • Atherosclerosis • Cocaine use (more common with type B)⁵ • Sudden withdrawal of beta blocker therapy • History of a bicuspid aortic valve or previous aortic valve surgery

Pearls of the History and Physical Examination

History

- Pain: present 95% of the time, onset is sudden (85%)⁴; abdominal in 33% of cases⁶; classic pain (tearing or ripping) only present in 50% of cases
- Syncope and stroke: occur 9%⁵ and 5%-15%, respectively
- Other organ involvement: bloody stools,³ anuria, anterior cord syndrome, paraplegia, or quadriplegia

Physical Examination

- Blood pressure: 33% normotensive on examination⁷; hypotension is associated with 50% overall mortality rate
- Diastolic murmur: 50% of type A dissections⁴
- Widened pulse pressure: 15%-38% of cases
- Signs of heart failure or pericardial tamponade may be present in type A dissections
- Pulse duplication (due to redundant flow from the false lumen) occurs uncommonly⁶
- Other organ involvement: absent bowel sounds,³ transverse myelitis, anterior cord syndrome, paraplegia, or quadriplegia

Diagnostic Studies and Laboratory Values

Blood Tests

- Lactic acidosis (lactate >2.4 mmol/dL) or transaminitis (threefold rise in enzymes) may indicate GI tract involvement³
- D-dimers were found to be positive retrospectively in seven patients with acute dissection^{2,8}
- Preliminary data: smooth muscle myosin chain serum levels may be specific and sensitive for acute dissection⁴

Electrocardiogram

- Shows nonspecific T-wave or ST-segment changes in 40% of cases⁴; normal in 31% of cases, but ST-segment elevation may occur as a result of myocardial infarction due to coronary ostial involvement in type A dissections

Imaging

- Chest x-ray: widened mediastinum present in about 60% of cases⁸
- Computed tomography (CT): quickest test (Sensitivity [Sn] 80%-100%, Specificity [Sp] 90%-100%)⁹
- Magnetic resonance imaging (MRI): better than CT, but speed and access may limit its usefulness (Sn 98%-100%, Sp 98%-100%).
- Echocardiogram: transesophageal echocardiography (TEE) adds to the diagnostic utility of transthoracic echocardiography (TTE) with its ability to visualize proximal coronary artery involvement and aortic regurgitation; it is favored over TTE when possible (TTE: Sn 60%-80%, Sp 90%-99%; TEE: Sn 80%-96%, Sp 85%-98%)
- Overall, a combination of CT with TTE or TEE is recommended for rapid diagnosis (CT) and assessment of dissection location as well as coronary involvement (echocardiogram).

Guide to Acute Management

- Lack of randomized placebo-controlled trials¹⁰

Type A Dissections

- Surgical emergency
- Medical management
 - Mortality rate: 20% at 1 day, 30% at 2 days, 40% at 1 week, 50% at 1 month (compared with surgical mortality rate: 10% at 1 day, 13% at 1 week, 20% at 1 month)⁵

- Optimal hemodynamics to improve surgical outcomes: target systolic blood pressure is approximately 110 mm Hg¹¹
 - Beta blockers are preferred (particularly esmolol); propranolol and labetalol have also been used with some success
 - Nitroprusside (0.3 µg/kg/min): can be added to beta blockers (must ensure beta blocker use concomitantly, as unopposed nitrate therapy can lead to reflex catecholamine release)⁴
 - Alternatives: diltiazem or verapamil if beta blockers are contraindicated⁵
 - Consider: trimethaphan (primary ganglionic blocker/direct vasodilator)
 - Morphine for pain relief
- If hypotension is present, ensure with echocardiography that tamponade and/or congestive heart failure is not present
- Pericardiocentesis for tamponade often fails (can accelerate bleeding and shock)
- Presurgical coronary angiography
 - IRAD database analysis suggests that a delay of 24 hours (for coronary angiography) before surgery is associated with better outcomes; this is largely understood to be a function of selection bias⁸
 - General opinion (based upon smaller studies) is that delay for angiography can only serve to put patients at additional risk¹²

Type B Dissections

- IRAD suggests better outcomes with medical management¹³
- Indications for surgery
 - Impending rupture
 - Organ ischemia due to branch vessel involvement
 - Propagation of dissection
 - Worsening pain despite optimal management¹⁴
 - Large, rapidly expanding false lumen¹⁵

- Endovascular grafting has been tried for type B dissections and appears to have similar rates of success as surgical repair; however, careful monitoring for late leakage or unseen tears must be performed⁵
- The pregnant patient with type B dissection
 - If <28 weeks, repair surgically (mortality ~80% without intervention)¹⁶
 - If >32 weeks, a cesarean section (C-section) with either simultaneous or staged repair is indicated
 - Decisions made between 28-32 weeks must be based on maternal and fetal status
 - Epidural anesthesia and labetalol infused at 1-10 µg/kg/min can be beneficial during labor/delivery; C-section anesthesia strategies are controversial
 - Medical management is identical to that of type A



Patient Care Warnings

- Continued beta blockade is the key to preventing adverse outcomes
- Follow-up imaging (CT or MRI) is indicated at 1, 3, 6, 9, and 12 months after initial incident, then yearly thereafter

References

- ② 1. Clouse WD, Hallett JW, Schaff HV, et al. Acute aortic dissection: Population-based incidence compared with degenerative aortic aneurysm rupture. *Mayo Clin Proc* 2004;79:176-80.
- ② 2. Nienaber CA, Fattori R, Mehta RH, et al. Gender-related differences in acute aortic dissection. *Circulation* 2004;109:3014-21.
- ③ 3. Chavan, A, Lotz J, Eolert F, et al. Endoluminal treatment of aortic dissection. *Eur J Radiol* 2003;13:2521-34.
- ③ 4. Kinaut AL, Cleveland JC. Aortic emergencies. *Emerg Med Clin North Am* 2003;21:817-45.
- ③ 5. Nienaber CA, Eagle KA. Aortic dissection: New frontiers in diagnosis and management: Part I: From etiology to diagnostic strategies. *Circulation* 2003;108:628-35.

- ③ 6. Bhalla S, Menias CO, Heiken JP. CT of acute abdominal aortic disorders. *Radiol Clin North Am* 2003;41:1153-69.
- ② 7. Tsai TT. Clinical characteristics of hypotension in patients with acute aortic dissection. *Am J Card* 2005;95:48-52.
- ② 8. Trimarchi S, Nienaber CA, Rampoldi V, et al. Contemporary results of surgery in acute type A aortic dissection: The International Registry of Acute Aortic Dissection experience. *J Thoracic Cardiovasc Surg* 2005;129:112-22.
- ③ 9. Mariani MA, D'Alfonso A, Nardi C, et al. Aortic dissection: Diagnosis, state-of-the-art of imaging and new management acquisitions. *Italian Heart J* 2004;5:648-55.
- ③ 10. Myrmet T, Lai DTM, Miller DC. Can the principles of evidence-based medicine be applied to the treatment of aortic dissections? *Eur J Cardio-Thoracic Surg* 2004;25:236-42.
- ③ 11. Nienaber CA, Eagle KA. Aortic dissection: New frontiers in diagnosis and management: Part II: Therapeutic management and follow-up. *Circulation* 2003;108:772-78.
- ② 12. Motellebzadeh R, Batas D, Oswaldo V, et al. The role of coronary angiography in acute type A aortic dissection. *Eur J Cardio-Thoracic Surg* 2004;25:231-35.
- ② 13. Suzuki T, Mehta RH, Ince H, et al. Clinical profiles and outcomes of acute type B aortic dissection in the current era: Lessons from the International Registry of Aortic Dissection (IRAD). *Circulation* 2003;108S:312-17.
- ② 14. Akutsu K, Nejima J, Kiuchi K. Effects of the patent false lumen on the long-term outcome of type B acute aortic dissection. *Eur J Cardio-Thoracic Surg* 2004;26:359-66.
- ② 15. Mehta RH, Bossone E, Evangelista A. Acute type B aortic dissection in elderly patients: Clinical features, outcomes, and simple risk stratification rule. *Ann Thoracic Surg* 2004;77:1622-28.
- ③ 16. Ray P, Murphy GJ, Shutt LE. Recognition and management of maternal cardiac disease in pregnancy. *Br J Anaesth* 2004;93:428-39.

ATRIAL FIBRILLATION AND FLUTTER

Definition, Etiology, and Epidemiology

Atrial Fibrillation

- Characterized by multiple wavelets of irregular atrial depolarizations at a rate of 350-600 impulses per minute with an irregular ventricular response
- Classified as¹:

- Paroxysmal: duration <7 days, self-terminating, can recur
- Persistent: duration >7 days, fails to self-terminate but terminated by cardioversion, can recur
- Permanent: duration >1 year with cardioversion that has failed or has not been attempted
- Lone: any of the above with no structural heart disease and age <60
- Atrial premature beats² can trigger fibrillation, with most ectopic beats originating near the pulmonary veins³
- Disease associations: hypertension (most common etiology),⁴ coronary disease, acute coronary syndromes (ACS),⁵ heart failure,⁶ rheumatic disease,⁷ hypertrophic cardiomyopathy,⁸ pulmonary embolism,⁹ chronic obstructive pulmonary disease (COPD),¹⁰ obesity,¹¹ hyperthyroidism, cardiac or intrathoracic surgery,¹² alcohol, caffeine,¹³ and familial¹⁴
- Increased prevalence among whites, male gender, or advanced age; cardioembolism may be responsible for 15%-20% of ischemic strokes¹⁵

Atrial Flutter

- Characterized by regular atrial depolarizations at a rate of 240-320 beats per minute and relatively predictable ventricular responses
- Classified as¹⁶:
 - Type I (isthmus-dependant): more common; macro-reentrant circuit bounded by the tricuspid annulus (TA), crista terminalis, and isthmus (tissue between the TA and inferior vena cava orifice); circuit is more commonly counterclockwise, but can also be clockwise
 - Type II: nonisthmus-dependent; less common
- Associated with right or left ventricular dysfunction, rheumatic heart disease (especially if mitral valve is involved), post cardiac surgery for repair of congenital defects, and any of the disorders that also cause

atrial fibrillation; primary atrial flutter can be seen in rare cases

- Rhythm is relatively stable but can revert to sinus rhythm or atrial fibrillation within hours to days; chronic flutter is uncommon and associated with atrial or ventricular enlargement

Pearls of the History and Physical Examination

History

- Symptoms consistent with rapid heart rate¹⁷; may be pronounced if arrhythmia coexists with left ventricular (LV) dysfunction
 - Palpitations, fatigue, lightheadedness, and dyspnea; less commonly syncope, angina, and hypotension
- Determine: time of onset, frequency, duration (<48 hours?), prior successful therapies, possible precipitating causes, coexistence of Wolff-Parkinson-White (WPW) syndrome, and presence or absence of pre-existing LV dysfunction¹⁷

Physical Examination

- Absence of A-wave in jugular venous pulsations seen in atrial fibrillation
- Flutter waves can be observed in jugular venous pulsation during atrial flutter
- Pulse: irregular in atrial fibrillation

Diagnostic Studies and Laboratory Values

Electrocardiogram

- Determine nature of atrial electrical activity and initially differentiate fibrillation from flutter; sinus P waves are absent in both entities
- Examine for pre-excitation: atrioventricular (AV) nodal blockade in this setting may result in preferential use of this accessory pathway and can lead to ventricular fibrillation

- Fibrillation: fibrillatory (f) waves (350-600 bpm), varying in amplitude, intervals, and morphology; irregularly irregular ventricular response (defined by R-R interval); differentiate from other disorders with irregular R-R intervals (multifocal atrial tachycardia, ectopic atrial tachycardia; see the section titled Narrow Complex Tachycardias)
- Flutter: in II, II, and AVF, observe biphasic saw-tooth flutter (F) waves (about 300 bpm), regular, usually no isoelectric interval in between. R-R interval is commonly half that of the atrial input in even ratios (A:V, 2:1, 4:1 ...); ratio greater than 2:1 in the absence of AV nodal blocking agents suggests AV nodal disease; lower ratio suggests accessory pathway or autonomic dysregulation

Laboratory Studies

- Thyroid function,¹⁷ troponins for ischemia/infarction, arterial blood gas (hypoxia), and others to identify possible etiology for arrhythmia

Echocardiogram¹⁷

- Define LV function/hypertrophy, atrial sizes, presence of pericardial disease, peak right ventricular pressure (pulmonary hypertension), and valvular abnormalities, all of which may help to identify possible etiologies; LV function can be impaired due to rapid rates (tachycardia-induced cardiomyopathy), so echocardiogram must be repeated after tachycardia is controlled
- Determine presence of intracardiac thrombus, which may dictate further management

Guide to Acute Management

- Synchronized external direct current cardioversion (DCCV) should be considered in the

hemodynamically unstable patient as first-line therapy¹⁷

- Acute rate control¹⁸
 - Normal LV function:
 - Beta blockers: metoprolol 5 mg IV over 2 minutes q 5 minutes $\times$ 3, then start oral formulation
 - Short-acting esmolol drip is an option to test patient compatibility if drug class adverse effects (bronchospasm) are feared
 - Calcium channel blockers: verapamil 5-10 mg IV over 2-3 minutes q 15-30 minutes; an infusion can be started thereafter
 - Diltiazem:¹⁹ first IV bolus of 0.25 mg/kg over 2 minutes; if ineffective, second bolus of 0.35 mg/kg over 2 minutes to be repeated 15 minutes later; continuous infusion at a rate of 5-15 mg/h in responders, but not in nonresponders
 - Digoxin is considered a last-line option as it is not as effective in the acute setting due to the slower onset of action compared with that of the aforementioned medications; it can be rapidly loaded IV (0.5 mg initially, 0.25 mg IV q 4-6 hours up to a total of 0.75-1.5 mg) or orally (method is similar except a total of 1-2 mg may be needed); maintenance oral therapy thereafter
 - Abnormal LV function
 - Digoxin: loaded as above; preferred in this context due to improvement in cardiac contractility and thus reduced reflex symptoms of low output and excess sympathetic tone²⁰
 - Amiodarone: not traditionally considered a drug for rate control but has been successfully used intravenously for this purpose in patients with tenuous hemodynamics¹⁸
- Atrial fibrillation (new-onset): further issues include rhythm control (reversion and maintenance of normal sinus), rate control, and prevention of cardioembolic phenomenon

CONVERSION TO NORMAL SINUS RHYTHM BASED UPON DURATION AND LV FUNCTION

<48 Hours Arrhythmia Duration

Unknown or >48 Hours Arrhythmia Duration

Normal LV Function¹⁸

- DCCV is successful 75%-93%, minimally proarrhythmic, and success inversely related to duration and left atrial size²¹
- Chemical cardioversion¹⁸
 - Amiodarone
 - Ibutilide
 - Flecainide
 - Propafenone
 - Procainamide
- No DCCV or chemical cardioversion due to risk of systemic embolization.
- Anticoagulate for 3 weeks with coumadin (INR 2-3), perform DCCV, and then continue to anticoagulate 1 month thereafter (due to electro-mechanical dissociation)
- Early cardioversion: place patient acutely on heparin, exclude cardiac thrombus by TEE, and perform DCCV within 24 hours, followed by 1 month of anticoagulation

Abnormal LV Function¹⁸

- DCCV or
- Amiodarone
- Anticoagulation
- DCCV

- 50% of patients with new atrial fibrillation convert spontaneously after 24 hours
- “Pill in the pocket”: patients with preserved LV function and paroxysmal atrial fibrillation who are converted to sinus rhythm with a single dose of flecainide or propafenone in the emergency department can be given a prescription for the effective medication to self-administer when symptoms of atrial fibrillation occur in the outpatient setting (94% effective)²²
- Rate vs. rhythm control: which one is superior?
 - AFFIRM trial suggests that rate control is comparable to rhythm control; rate control may be better in some

instances due to adverse side effects of antiarrhythmic drugs (AADs)²³

- Even in instances of rhythm control, high-risk patients (advanced age >60, hypertension, coronary disease, enlarged left atrium, depressed LV function) were more prone to strokes; therefore, anticoagulation should be administered indefinitely in this group²³
- If rhythm control is pursued, amiodarone is more effective at 1 year than sotalol or class I agents without cardioversion²⁴
- AFFIRM applies to asymptomatic patients; symptomatic patients usually feel better in normal sinus rhythm; in patients with ischemic disease with persistent atrial fibrillation, amiodarone is superior to sotalol for maintaining sinus rhythm, although both are efficacious for conversion to sinus rhythm²⁵
- Nonpharmacological approaches in refractory patients include pulmonary vein isolation/ablation, AV node ablation, permanent pacemaker placement, and other surgical techniques²⁶
- Atrial flutter
 - DCCV: Compared with atrial fibrillation, lower voltages might be effective (<50 J); however, cardioversion may result in atrial fibrillation, which will require a repeat shock at a higher voltage²⁷
 - Rapid atrial pacing: performed with a catheter in the esophagus; can terminate atrial flutter but is painful and not readily available²⁸
 - Ibutilide is the intravenous drug of choice for chemical conversion²⁹; especially effective in atrial fibrillation/flutter of duration under 96 hours and is more effective for flutter compared with atrial fibrillation
 - Anticoagulation (see table)
- Anticoagulation in chronic atrial fibrillation and flutter: to prevent cardioembolic disease, targeted INR 2-3 with coumadin therapy for all patients except

those with lone fibrillation; flutter is treated similarly¹

- The CHADS₂ stroke risk index can help quantify the risk for stroke in patients with atrial fibrillation and aid in selection of antithrombotic therapy. 1 point is assigned for congestive heart failure, hypertension, age >75, or diabetes mellitus; 2 points are assigned for prior cerebrovascular accident or transient ischemic attack³⁰
- Stroke rate per 100 patient-years without antithrombotic therapy increases by a factor of 1.5 for every 1 point increment in the CHADS₂ score



Patient Care Warnings

- If hemodynamic instability is apparent, synchronized DCCV should be performed immediately; ask questions later
- Determine presence of pre-excitation whenever possible; best therapy for WPW is DCCV
- Knowing LV function is crucial to many decisions

References

- ③ 1. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. *J Am Coll Cardiol* 2001;38:1231.
- ② 2. Kolb C, Nurnberger S, Ndrepepa G, et al. Modes of initiation of paroxysmal atrial fibrillation from analysis of spontaneously occurring episodes using a 12-lead Holter monitoring system. *Am J Cardiol* 2001;88(8):853-57.
- ① 3. Chen SA, Hsieh MH, Tai CT, et al. Initiation of atrial fibrilla-

- tion by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. *Circulation* 1999;100:1879-86.
- ② 4. Kannel WB, Abbott RD, Savage DD, et al. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med* 1982;306:1018-22.
 - ① 5. Crenshaw BS, Ward SR, Granger CB, et al. Atrial fibrillation in the setting of acute myocardial infarction: The GUSTO-I experience. Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. *J Am Coll Cardiol* 1997;30:406-13.
 - ① 6. Carson PE, Johnson GR, Dunkman WB, et al. The influence of atrial fibrillation on prognosis in mild to moderate heart failure: The V-HeFT Studies. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;87(6 Suppl):102-10.
 - ② 7. Diker E, Aydogdu S, Ozdemir M, et al. Prevalence and predictors of atrial fibrillation in rheumatic valvular heart disease. *Am J Cardiol* 1996;77:96-98.
 - ② 8. Robinson K, Frenneaux MP, Stockins B, et al. Atrial fibrillation in hypertrophic cardiomyopathy: A longitudinal study. *J Am Coll Cardiol* 1990;15:1279-85.
 - ③ 9. Weber DM, Phillips JH Jr. A re-evaluation of electrocardiographic changes accompanying acute pulmonary embolism. *Am J Med Sci* 1966;251:381.
 - ② 10. Buch P, Friberg J, Scharling H, et al. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J* 2003;21:1012-16.
 - ② 11. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;292:2471-77.
 - ② 12. Vaporciyan AA, Correa AM, Rice DC, et al. Risk factors associated with atrial fibrillation after noncardiac thoracic surgery: Analysis of 2588 patients. *J Thorac Cardiovasc Surg* 2004;127:779-86.
 - ② 13. Ettinger PO, Wu CF, De La Cruz C Jr, et al. Arrhythmias and the "holiday heart": Alcohol-associated cardiac rhythm disorders. *Am Heart J* 1978;95:555.
 - ③ 14. Darbar D, Herron KJ, Ballew JD, et al. Familial atrial fibrillation is a genetically heterogeneous disorder. *J Am Coll Cardiol* 2003;41:2185-92.
 - ② 15. Tribolet de Abreu T, Mateus S, Correia J. Therapy implications of transthoracic echocardiography in acute ischemic stroke patients. *Stroke* 2005.
 - ② 16. Wells JL Jr, MacLean WA, James TN, et al. Characterization of atrial flutter: Studies in man after open heart surgery using fixed atrial electrodes. *Circulation* 1979;60:665
 - ③ 17. Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology

Committee for practice guidelines and policy conferences. Developed in collaboration with the North American Society of Pacing and Electrophysiology. *Circulation* 2001;104:2118-50.

- ③ 18. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 6: advanced cardiovascular life support: 7D: the tachycardia algorithms. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. *Circulation* 2000;102 (8 Suppl):1158-65.
- ① 19. Salerno D, Dias V, Kleiger R, et al. Efficacy and safety of intravenous diltiazem for treatment of atrial fibrillation and atrial flutter. The Diltiazem-Atrial Fibrillation/Flutter Study Group. *Am J Cardiol* 1989;63:1046-51.
- ③ 20. Sarter B, Marchlinski F. Redefining the role of digoxin in the treatment of atrial fibrillation. *Am J Cardiol* 1992;69:71-78; discussion 78-81.
- ② 21. Gallagher M, Guo X, Poloniecki J, et al. Initial energy setting: Outcome and efficiency in direct current cardioversion of atrial fibrillation and flutter. *J Am Coll Cardiol* 2001;38:1498-1504.
- ① 22. Alboni P, Botto GL, Baldi N, et al. Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. *N Engl J Med* 2004;351:2384-91.
- ① 23. Wyse DG, Waldo AL, DiMarco JP, et al. Atrial fibrillation follow-up: Investigation of Rhythm Management (AFFIRM) Investigators: A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.
- ② 24. AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: An AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol* 2003;42:20-29.
- ① 25. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;352:1861-72.
- ③ 26. Lee J. Atrial fibrillation: The nonpharmacologic strategy. *Mt Sinai J Med* 2002;69:232-41.
- ③ 27. Resnekov L. Cardiac arrhythmias: Present status of electroversion in the management of cardiac dysrhythmias. *Circulation* 1973;47:1356.
- ③ 28. Braunwald E. *Heart Disease*, 6th ed. W.B. Saunders, Philadelphia, 2001:830-55.
- ① 29. Ellenbogen K, Stambler B, Wood M, et al. Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: A dose-response study. *J Am Coll Cardiol* 1996;28:130-36.
- ② 30. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke. *JAMA* 2001;285:2864-70.

INFECTIVE ENDOCARDITIS

Definition, Etiology, and Epidemiology

- Microbial infection of the endocardial surface of the heart, including but not limited to the heart valves
- Acute endocarditis increasingly more common with increase in intravenous drug use (IVDU), elderly patient population, presence of indwelling intravenous lines, and hemodialysis
- Incidence: 1.7 to 6.2 cases per 100,000 person-years, increasing to 150-2000 cases per 100,000 person-years in IVDU¹
- Pre-existing cardiac disease exists in majority of patients who develop infective endocarditis (IE); however, only 10%-30% of patients with IE from IVDU have underlying cardiac disease

PREDISPOSING CONDITIONS	
High Risk	Moderate Risk
• Prosthetic heart valves • Prior IE	• Other congenital heart disease (exception is secundum atrial septal defect; no increased risk for IE)
• Cyanotic congenital heart disease	• Mitral valve prolapse with thickened leaflets or regurgitation
• Surgically constructed systemic to pulmonary shunts	• Hypertrophic obstructive cardiomyopathy acquired valvular heart disease

- Microbiological features: staphylococcal species (*S. aureus* and coagulase-negative) are the most common etiologies

NATIVE VALVE ENDOCARDITIS*

Organism	Native-valve IE	Native-valve IE in IVDU	Relevant Clinical History
Streptococcal species	31%	8%	<i>S. viridans</i> : dental procedure, poor dental hygiene
<i>S. aureus</i>	44%	69%	IVDU or IV access devices
Coagulase-negative staphylococcus	6%		Hemodialysis; IVDU
Enterococcus species	8%	2%	Genitourinary procedure or GI malignancy/procedure
Other bacteria	4%	5%	
Culture-negative	6%	5%	
HACEK†	4%		
Fungal	1%	2%	IVDU; immunosuppression; long-term intravenous access

*Adapted from references 1, 2, and 13

†HACEK: *Haemophilus parainfluenza* and *aphrophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*

PROSTHETIC VALVE ENDOCARDITIS (PERCENTAGE OF ALL CASES BY TIME POSTOPERATIVELY)*

Organism†	Early <60 d	Intermediate 60 d-12 mo	Late > 12 mo
Streptococcal species	1	7-10	30-33
<i>S. aureus</i>	20-24	10-15	15-20
Coagulase-negative staphylococcus	30-35	30-35	10-12
Enterococcus species	5-10	10-15	8-12
Gram-negative bacilli	10-15	2-4	4-7
Fungal	5-10	10-15	1
Culture-negative/HACEK‡	3-7	3-7	3-8

*Adapted from references 1, 2, and 13

†Other microbiological considerations: *Bartonella*, *Brucella*, *Legionella*, *Coxiella*, and *Chlamydia*

‡HACEK: *Haemophilus parainfluenza* and *aphrophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*

Pearls of the History and Physical Examination

History

- Predisposing conditions noted above
- History of preexisting valvular disease
- Recent procedure where transient bacteremia may have occurred
- Presentation may be in form of complications of IE
 - Congestive heart failure
 - Neurological findings from embolic stroke or mycotic aneurysm formation/rupture
 - Heart block from extravalvular extension of infection into conduction system
 - Osteomyelitis/arthritis (especially with axial skeleton involvement and multiple joints)
- Fever

Physical Examination

- Fever: present in 90% of patients (may be absent in patients with comorbidities such as renal failure, advanced age, and infections with coagulase-negative staphylococcus)
- Cardiac murmur present at some time during course in 80% of patients
- Vascular phenomena: arterial emboli, conjunctival hemorrhage, Janeway's lesions, pulmonary infarction (pleuritic chest pain), splenic infarction (left upper quadrant or referred left shoulder pain)
- Immunological phenomena: Osler's nodes, Roth's spots, hematuria, evidence of proteinuria

Diagnostic Studies and Laboratory Values

- Definite endocarditis: (1) positive histology or culture from vegetation, (2) two major criteria, (3) one major and three minor criteria, or (4) five minor criteria
 - Rejected diagnosis: (1) firm alternative diagnosis established or (2) resolution after ≤ 4 days of antibiotic therapy

DUKE CRITERIA FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS⁵

Major Criteria	Minor Criteria
• Positive blood cultures (≥ 2 of 2) with microbe typical for infective endocarditis (<i>Streptococcus aureus</i>, community-acquired enterococci, <i>S. bovis</i>, <i>S. viridans</i>, HACEK group, single positive culture for <i>C. burnetti</i> or antibody titre against phase I $> 1:800$), or persistently positive blood cultures with compatible microbe • Evidence of endocardial involvement: new significant valve regurgitation (new or worsening murmur not sufficient), oscillating intracardiac mass, abscess, or new partial prosthetic valve dehiscence	• Predisposing cardiac condition or IVU • Fever $\geq 38.0^{\circ}\text{C}$ (100.4°F) • Vascular phenomena • Immunological phenomena • Echocardiogram consistent with endocarditis but not meeting major criteria • Positive blood culture but not meeting major criteria, or positive serology for compatible microbe

Sensitivity 83%, specificity 99%, negative predictive value (NPV) 92% for IE < PE

- Blood tests
 - Complete blood count: leukocytosis, anemia, hemolysis with prosthetic valve dehiscence
 - Urinalysis: may see hematuria
 - Serological testing for culture-negative organisms (*Bartonella* species, *Brucella* species, *Chlamydia* species, *Coxiella burnetti*, *Legionella* species, *Mycoplasma* species, *Tropheryma whippelii*)

Electrocardiogram

- Heart block or new conduction abnormality with perivalvular extension

Chest Radiograph

- Pulmonary congestion with left-sided endocarditis causing left ventricular dysfunction, septic emboli with right-sided lesions

Echocardiography

- May detect vegetation on valve, ruptured/perforated valve, intracardiac fistulae, abscess formation, prosthetic valve dehiscence
- Negative predictive value (NPV) of TEE high

	TTE*		TEE*	
	Sn (Percentage)	Sp (Percentage)	Sn (Percentage)	Sp (Percentage)
Native valve	50-60	95	92	95
Prosthetic valve	25	100	82-96	97
Abscess	30	99	87	95

*Adapted from references 6-10

- Consider TEE for suspected IE, either as initial imaging or follow-up evaluation in the following situations^{3,11,12}

High-Risk Patients*	Evaluation for Complications*
Prosthetic valve endocarditis	Poor response to antibiotics
Prior endocarditis	Suspicion for abscess
<i>S. aureus</i> bacteremia	New heart block
Congenital heart disease	New heart murmur
Presence of indwelling catheters	Congestive heart failure
Fungal infections	

*Adapted from reference 12

Guide to Acute Management

- Cornerstone of therapy is isolation of causative organism with susceptibility testing
- Draw three sets of blood cultures, with the first and last set at least 1 hour apart; bacteremia continuous and low-level; the greater volume of blood cultured (60 mL total) leads to better yield

EMPIRIC ANTIBIOTIC THERAPY WHILE CULTURES PENDING IF PATIENT APPEARS ACUTELY ILL

Native Valve	Prosthetic Valve
Combination of penicillin and gentamicin or vancomycin and gentamicin in areas of methicillin-resistant staphylococcus aureus prevalence	Vancomycin and gentamicin +/- rifampin

ANTIBIOTIC THERAPY BASED ON ORGANISM¹

Microorganism	Native Valve	Prosthetic Valve
PCN-susceptible <i>S. viridans</i> and <i>S. bovis</i>	Pen G or ceftriaxone × 4 weeks	Pen G × 6 weeks and gentamicin × 2 weeks
Relative penicillin (PCN)-resistant streptococci	Pen G × 4 weeks and gentamicin × 2 weeks	Pen G × 6 weeks and gentamicin × 6 weeks
<i>Streptococcus</i> species with PCN resistance, <i>Enterococcus</i> species	Pen G (or ampicillin) and gentamicin × 4-6 weeks	Pen G (or ampicillin) and gentamicin × 6 weeks
Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA)	Nafcillin or oxacillin × 4-6 weeks with possible addition of gentamicin for first 3-5 days of therapy	Nafcillin or oxacillin with rifampin × 6 weeks and gentamicin × 2 weeks
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Vancomycin × 4-6 weeks with possible addition of gentamicin for first 3-5 days of therapy	Vancomycin with rifampin × 6 weeks and gentamicin × 2 weeks
HACEK* organisms	Ceftriaxone × 4 weeks	Ceftriaxone × 6 weeks

*HACEK: *Haemophilus parainfluenza* and *aphrophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*

- Commonly accepted indications for surgical intervention^{1,3,11,12} (surgical intervention required in 25%-30% of cases in the acute phase¹¹)
 - Congestive heart failure with evidence of valvular dysfunction
 - Persistent infection defined by bacteremia or fever after 7 days of appropriate antimicrobial therapy
 - Recurrent emboli in setting of adequate therapy
 - Extension of infection including fistulae, abscess, pericardial involvement
 - Difficult to treat organisms such as *Pseudomonas*, fungal infections, *Coxiella*, or no effective antimicrobial therapy
 - Prosthetic valve malfunction or evidence of instability (rocking prosthesis or evidence of paravalvular leak)
 - Early prosthetic valve endocarditis (<2 months postoperatively)
- The American Heart Association guidelines for antibiotic prophylaxis are based on risk of complications if endocarditis were to occur⁴



Patient Care Warnings

- Consider IE in any patient with prosthetic valve and unexplained fever; fever may be absent in early prosthetic valve infections
- Rule out IE in any patient with prosthetic valve dehiscence, even without evidence of systemic infection
- No role for anticoagulation in native valve endocarditis³; may increase mortality; anticoagulation only if indicated for other reasons (e.g., mechanical valves)

References

- ③ 1. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *New Engl J Med* 2001;345:1318-30.
- ③ 2. Watkin RW, et al. The microbial diagnosis of infective endocarditis. *J Infect Dis* 2003;47:1-11.
- ③ 3. Bayer A, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998;98:2936-48.
- ③ 4. Dajani AS, et al. Prevention of bacterial endocarditis: Recommendations by the American Heart Association. *Circulation*. 1997;96:358-66.
- ② 5. Durack DT, et al. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. *Am J Med* 1994; 96:200-209.
- ① 6. Shively BK, et al. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. *J Am Coll Cardiol* 1991;18:391-97.
- ① 7. Daniel WG, et al. Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic positions. *Am J Cardiol* 1993;71:210-15.
- ① 8. Daniel WG, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. *New Engl J Med* 1991;324:795-800.
- ③ 9. Sachdev M, Peterson GE, Jollis J. Imaging techniques for diagnosis of infective endocarditis. *Cardiol Clin* 2003;21:185-95.
- ② 10. Morguet AJ, Werner GS, et al. Diagnostic value of transesophageal compared with transthoracic echocardiography in suspected prosthetic valve endocarditis. *Herz* 1995;20:390-98.
- ③ 11. Olaison L, Pettersson G. Current best practice guidelines: Indications for surgical intervention in infective endocarditis. *Cardiol Clin* 2003;21:235-51.
- ③ 12. Mauri L, de Lemos JA, O'Gara PT. Infective endocarditis. *Curr Probl Cardiol* 2001;26:562-610.
- ③ 13. Moreillon P, Que Y-A. Infective endocarditis. *Lancet* 2004; 363:139-49.

PERICARDIAL EFFUSION AND CARDIAC TAMPONADE

Definition, Etiology, and Epidemiology

- The pericardium is a two-layered sac comprising the visceral pericardium, firmly adhered to the epicardium, and the parietal pericardium; between the

two layers is a potential space containing a small amount of fluid

- Pericardial effusion results from accumulation of fluid in this space; fluid is well tolerated hemodynamically if it accumulates slowly
- Cardiac tamponade with hemodynamic compromise occurs if accumulation is rapid, even in settings of small volume effusions

MOST COMMON CAUSES OF LARGE PERICARDIAL EFFUSIONS¹⁻³

Neoplastic	Most common; due to spread of locally adjacent cancer (lung or breast); renal, Hodgkin's lymphoma, melanoma most commonly
Idiopathic	Second most common; perhaps residual sequelae of prior viral pericarditis; presence of a large effusion without underlying cause, inflammatory signs, or tamponade was predictive of chronic idiopathic effusion in one trial ⁴
Tuberculosis	Rare in developed countries
Fungal	Histoplasmosis most common in endemic areas; <i>Candida</i> , <i>Aspergillus</i> , <i>Blastomycosis</i> , <i>Nocardia</i> , and <i>Actinomyces</i> in immunocompromised hosts
Uremic	
Connective tissue disease	Rheumatoid arthritis, systemic lupus erythematosus, and scleroderma
Hypothyroidism	Typically with myxedema
Other	Trauma and postoperative inflammation (postpericardiotomy syndrome)

Pearls of the History and Physical Examination^{1,3}

History

- Predisposing conditions as noted above
- Chest pain or pressure without typical features of ischemia
- Dyspnea without orthopnea or paroxysmal nocturnal dyspnea

- Palpitations
- Compressive symptoms: dysphagia with esophageal compression, hiccups from phrenic nerve involvement, hoarseness from involvement of recurrent laryngeal nerve

Physical Examination³

- Tachycardia (50%), tachypnea
- Elevated jugular venous pressure (45%)
- Distant heart sounds (muffled S₁ and S₂)
- Peripheral edema (35%), hepatomegaly
- Cardiac tamponade: hypotension, raised jugular venous pressure, muffled heart sounds (Beck's triad) observed most often with rapid accumulation of fluid as occurs in trauma;
 - Pulsus paradoxus is an exaggeration of normal decrease in left ventricular stroke volume with inspiration, greater than 10 mm Hg by sphygmomanometry (present in approximately 77%-80% of patients with tamponade)⁴; may be absent in very low cardiac output states⁶ and can be seen in other settings such as pulmonary disease

Diagnostic Studies and Laboratory Values

- Complete blood count: leukocytosis, which may be profound depending upon underlying cause
- Cardiac markers of ischemia are generally negative unless a significant component of myocarditis is also present
- Elevation in nonspecific markers of inflammation, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Viral or fungal serology
- Sputum for acid-fast bacilli (AFB) or purified protein derivative (PPD) skin test
- Pericardial fluid for Gram's stain and culture, AFB, cholesterol, total protein, lactate dehydrogenase,

adenosine deaminase, cytology (diagnostic yield is often low)

- Pericardial biopsy may have greater yield for diagnosis
- Chest x-ray: enlarged, classically “spherical” or “globular” cardiomeastinal silhouette with clear lung fields; characteristic findings of pulmonary tuberculosis or histoplasmosis may be seen
- Electrocardiogram: low-voltage QRS; electrical alternans
- Echocardiography: confirms presence of excess fluid in pericardial sac; dilated inferior vena cava with loss of normal inspiratory collapse; swinging heart
- Pulmonary artery catheter: rapid x-descent due to restrictive filling and loss of y-descent; in tamponade: elevation and equalization of RA, RV, and PA pressures within 5 mm Hg of one another

Guide to Acute Management

- Cardiac tamponade with evidence of hemodynamic instability: begin aggressive volume resuscitation to elevate intracardiac pressures to greater than pericardial pressures; emergent therapeutic pericardiocentesis with or without imaging if impending circulatory collapse⁶
- Treat underlying condition if known
- Monitor closely for development of tamponade physiology
- No indication for emergent drainage of large asymptomatic pericardial effusion but may consider on elective, controlled basis as tamponade physiology can occur at any time⁵
- May consider indwelling catheter drainage or pericardial window if recurrent effusion develops, or for palliation in setting of malignant effusions



Patient Care Warnings

- Avoid diuresis and positive pressure ventilation in a patient with suspected tamponade
- No indication for emergent pericardiocentesis in patients with asymptomatic pericardial effusion
- Use echocardiographic or fluoroscopic guidance whenever possible to guide pericardiocentesis

References

1. Braunwald E. Heart Disease, 6th ed. Philadelphia, W.B. Saunders, 2001.
2. Aikat S, Ghaffari S. A review of pericardial diseases: Clinical, ECG and hemodynamic features and management. *Cleve Clin J Med* 2000;67:903-14.
3. Karam N, et al. Diagnosis and management of chronic pericardial effusions. *Am J Med Sci* 2001;322:79-87.
4. Sagristá-Sauleda J, et al. Clinical clues to the causes of large pericardial effusions. *Am J Med Sci* 2000;109:95-101.
5. Sagristá-Sauleda J, et al. Long-term follow-up of idiopathic chronic pericardial effusion. *N Engl J Med* 1999;341:2054-59.
6. Spodick DH. Acute cardiac tamponade. *N Engl J Med* 2003;349:684-90.

ACUTE PERICARDITIS

Definition, Etiology, and Epidemiology

- The pericardium consists of two layers: the inner visceral layer attached to the epicardium and an outer parietal layer
- Acute pericarditis is an acute inflammation of the pericardium with or without a pericardial effusion
- Acute pericarditis is common but often unrecognized due to its self-limited course (true incidence unknown)

- Acute pericarditis <6 weeks; subacute 6 weeks to 6 months; chronic >6 months

ETIOLOGY^{1,2}

Type	Comment
Idiopathic	Most common cause
Viral	Coxsackievirus, echovirus, influenzae, Epstein-Barr, varicella, hepatitis, mumps, and HIV; responsible for almost as many cases as idiopathic.
Tuberculosis	Rare in developed countries
Bacterial	Rare; usually as complication of existing cardiopulmonary disease: streptococci, staphylococci, gram-negative rods
Fungal	Histoplasmosis most common in endemic areas; <i>Candida</i> , <i>Aspergillus</i> , <i>Blastomycosis</i> , <i>Nocardia</i> , and <i>Actinomyces</i> in immunocompromised hosts
Uremic	
Connective tissue disease	Rheumatoid arthritis, systemic lupus erythematosus, and scleroderma.
Drugs	Drug-induced lupus: hydralazine, methyldopa, procainamide
Post-myocardial infarct (MI)	2-5 days post-MI as an inflammatory response to transmural myocardial injury
Postcardiotomy	Second week to second month post operation
Dressler's syndrome	Weeks to several months after MI or open heart surgery; believed to be autoimmune phenomenon
Neoplastic	Due to spread of locally adjacent cancer (lung or breast); renal, Hodgkin's lymphoma, melanoma
Radiation	Typically within 1 year of treatment

Pearls of the History and Physical Examination^{3,4}

History

- Recent viral illness, travel history to endemic areas, recent MI or angina, recent sternotomy, history of malignancy or radiation therapy

- Sharp retrosternal pain that may radiate to the back; often aggravated by lying down or inspiration and relieved by sitting up
- Trapezial ridge pain transmitted through the phrenic nerve is virtually pathognomonic for pericardial pain³
- Fever, malaise, or myalgias

Physical Examination

- Pericardial friction rub: involves both ventricular systole and diastole but can be evanescent, requiring frequent examinations; normal S₁ and S₂

Diagnostic Studies and Laboratory Values

Blood Tests

- Complete blood count (CBC): leukocytosis, which may be profound depending on underlying cause
- Cardiac markers of ischemia generally negative unless a significant component of myocarditis
- Elevation in nonspecific markers of inflammation, such as erythrocyte sedimentation rate and C-reactive protein
- Viral or fungal serology
- Sputum for acid-fast bacilli or purified protein derivative (PPD) skin test
- Thyroid function tests

Chest X-Ray

- Usually normal cardiomedastinal silhouette unless concurrent pericardial effusion; characteristic findings of pulmonary tuberculosis or histoplasmosis

Electrocardiogram (ECG)

- Diffuse ST elevation and PR depression; often difficult to differentiate from acute ischemia and early repolarization

Electrocardiographic Feature	Acute Pericarditis	Acute MI	Early Repolarization
ST-segment concavity	Upward	Downward	Upward
Loss of R waves Presence of Q waves Reciprocal changes	Absent	Present	Absent
PR-segment elevation	Specific to acute pericarditis when involving aVR	Absent	Absent
ST to T amplitude in V ₆	>0.25	<0.25	<0.25
T-wave inversion	After J point normalized to baseline	While ST segment still elevated	Absent

Adapted from references 1,3, and 5

Guide to Acute Management

- Treat underlying condition if known
- Pericardiocentesis or pericardial biopsy not routinely indicated for diagnosis of acute pericarditis
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Corticosteroids in patients who fail or have contraindication to NSAIDs
- Colchicine has shown some efficacy in patients with idiopathic recurrent pericarditis⁶
- Monitor for complications: development of effusion and/or tamponade, recurrent pericarditis



Patient Care Warnings

- Pericardiocentesis not routinely indicated in diagnosis of acute pericarditis

References

- ③ 1. Aikatt S, Ghaffari S. A review of pericardial diseases: Clinical, ECG and hemodynamic features and management. *Cleve Clin J Med* 2000;67:903-14.
- ③ 2. Oakley CM. Myocarditis, pericarditis and other pericardial diseases. *Heart* 2000;84:449-54.
- ③ 3. Braunwald E. *Heart Disease*, 6th ed. Philadelphia, W.B. Saunders, 2001:1833-36.
- ③ 4. Hoit BD. Pericardial heart disease. *Curr Probl Cardiol* 1997;22:353-400.
- ③ 5. Wang K, et al. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003;349:2128-35.
- ① 6. Adler Y, et al. Colchicine treatment for recurrent pericarditis: A decade of experience. *Circulation* 1998;97:2183-85.

NARROW COMPLEX TACHYCARDIA

Definition, Etiology, and Epidemiology

- Defined as rhythms with rates greater than 100 beats per minute and QRS duration <120 msec
- Includes many arrhythmias but can be distinguished by characteristics
 - Regular or irregular ventricular response
 - Long or short RP interval: defined as less than half the RR interval (short) or greater than half the RR interval (long)

Arrhythmia	Clinical Characteristics	ECG Characteristics
Irregular		
atrial fibrillation	Increasing incidence with age, 10% >85 years old	Observe wavelets on atrial tracing without organized activity
Multifocal atrial tachycardia	Often seen with underlying pulmonary or heart disease	Three or more distinct P-wave morphologies and a variable PR interval
Atrial flutter with variable response	Usually with conditions that cause right atrial dilation.	Sawtooth P waves but irregular ventricular

Arrhythmia	Clinical Characteristics	ECG Characteristics
Regular Short RP • Atrioventricular nodal reentrant tachycardia (AVNRT) • AVRT • Junctional tachycardia Long RP • Sinus tachycardia • Ectopic atrial tachycardia • Atypical AVNRT Atrial flutter with fixed response		response can be observed due to variable conduction P waves hidden in QRS; if visible, negative in inferior leads Often see preexcitation of ventricles (delta wave) when in sinus rhythm (Wolff-Parkinson-White [WPW] syndrome¹) See retrograde P waves from AV depolarization. Typical P waves before each QRS Unusual P-wave axis, single P-wave morphology Inverted P waves. Sawtooth appearance of flutter waves, rates 240-320 bpm
	Increasing incidence with age, 70% female, more common than AV reentrant tachycardia (AVRT)	
	Most often occurs in younger patients with accessory pathways	
	Rare; occurs with rheumatic heart disease, ischemic heart disease, digoxin toxicity, etc.	
	Should raise concern for underlying reason (pulmonary embolus, withdrawal, pain, infection, etc.)	
	Often associated with digitalis toxicity or cardiac disease	
	Rare; occurs in 10% of AVNRT; initiated by premature ventricular contractions instead of premature atrial contractions (PACs)	
	Usually with conditions that cause right atrial dilation; most often 2:1 ventricular response	

Adapted from references 2 and 3

Etiology of Common Narrow Complex Tachycardias

- Atrial fibrillation: see section titled Atrial Fibrillation and Flutter
- Atrial flutter: see section titled Atrial Fibrillation and Flutter
- AVNRT
 - Two separate bidirectional pathways around the AV node
 - One conducts FAST with LONG refractory period; the other conducts SLOW with SHORT refractory period
 - In sinus rhythm, conduction occurs down the FAST pathway
 - Arrhythmia typically initiated by a PAC that conducts down the SLOW pathway, spreads to ventricles, and encircles AVN back up the FAST pathway³
- AVRT
 - Abnormal accessory pathway located away from the AV node, along the atrioventricular ring
 - Most pathways conduct retrograde only, however some are bidirectional
 - Typically initiated by PAC or PVC that begins circular conduction that travels anterograde down AVN to bundle of His, Purkinje's fibers, then retrograde up the accessory pathway³
- WPW syndrome: the combination of AVRT plus a delta wave during sinus rhythm

Pearls of the History and Physical Examination

History

- Risk factors: previous myocardial infarction, angina, hypertension, thyroid disease, rheumatic heart disease, and medication profile (digoxin and other antiarrhythmics)
- Symptoms span the spectrum from asymptomatic to symptoms of pulmonary edema; most patients experience palpitations and fatigue

Physical Examination

- Signs of heart failure, including distended neck veins, heart rate regularity, pulmonary congestion, and lower extremity edema; all patients need to be closely monitored for hemodynamic stability with frequent blood pressure checks

Diagnostic Studies and Laboratory Values

Blood Tests

- Serum chemistries: abnormalities of potassium or magnesium, cardiac ischemia markers, thyroidstimulating hormone (hyperthyroidism), and digoxin level (toxicity)
- Complete blood count: anemia

Electrocardiogram

- In order to accentuate the P waves, Lewis leads may be used (arm leads are placed over the sternum)
- Often a longer rhythm strip is required for proper evaluation; always keep a rhythm strip running when administering therapeutic or diagnostic medications
- Adenosine can unmask flutter waves (see the following Guide to Acute Management and Patient Care Warnings)

Echocardiogram

- Perform when the patient is stable
- Diagnostic clues include evidence of congestive heart failure, valvular abnormalities, atrial dilation, and wall motion abnormalities

Guide to Acute Management^{2,3}

- Atrial fibrillation: see section titled Atrial Fibrillation and Flutter
- Atrial flutter: see section titled Atrial Fibrillation and Flutter
- Multifocal atrial tachycardia: ensure potassium (4.0)

and magnesium (2.0) are properly supplemented; main intervention is treatment of underlying pulmonary (or cardiac) disease; if direct therapy is required, beta blockers and calcium channel blockers are used primarily

- Regular supraventricular tachycardia (SVT): initial therapy focuses on slowing the rate
 - Vagal maneuvers (Valsalva, carotid massage, cold water) are often successful
 - AV nodal blockade can be accomplished with IV adenosine 6 mg (up to 18-mg dose if first dose unsuccessful) or IV verapamil 5 mg $\times$ 3q5 min

LONG-TERM MEDICAL MANAGEMENT

Arrhythmia	First-Line Therapy	Second-Line Therapy
AVNRT	CCBs, BBs, digoxin	Catheter ablation
AVRT (no WPW)	Catheter ablation	CCBs, BBs, digoxin
WPW	Catheter ablation	Class IA, Class IC
Atrial Tachycardia	CCBs, BBs, digoxin	Class IC, Catheter ablation

class IA: quinidine, procainamide, disopyramide; class IC: flecanainide, propafenone^{2,3};
BBs = beta blockers; CCBs = calcium channel blockers



Patient Care Warnings

- Patients with atrial fibrillation and WPW should not be given nodal blockers to avoid inducing 1:1 conduction down the accessory pathway and subsequent VT; agents that slow ventricular conduction such as procainamide are preferred
- Adenosine
 - Theoretical risk of bronchospasm in patients with asthma should always be considered
 - Always have defibrillation paddles available when using adenosine

References

- ② 1. Wolff L, Parkinson J, White PD. Bundle-branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. *Am Heart J* 1930;5:685.
- ③ 2. Braunwald E. *Heart Disease*, 6th ed. Philadelphia, WB Saunders, 2001:830-55.
- ③ 3. Ganz L, Freidman P. Supraventricular tachycardia. *N Engl J Med* 1995;332:162-73.

WIDE COMPLEX TACHYCARDIA

Definition, Etiology, and Epidemiology

- Defined as rhythms with rates greater than 100 bpm and QRS duration >120 msec

DIFFERENTIAL DIAGNOSIS OF WIDE COMPLEX TACHYCARDIA (WCT)¹

Arrhythmia	Characteristics
Supraventricular tachycardia (SVT) with bundle branch block or aberrancy	WCT dependent on rate-related conduction block within right or left bundle of His/Purkinje's fibers; 21% of WCT cases ²
Supraventricular tachycardia with conduction over accessory path (i.e. Wolff-Parkinson-White [WPW] syndrome)	In the setting of WPW, patients can have pre-excited atrial fibrillation (AF) (with conduction over accessory path) or antidromic atrioventricular (AV) reentry tachycardia causing WCT. Preexcited AF has the propensity to initiate ventricular fibrillation (VF).
Ventricular tachycardia	Most common cause of WCT ² (~80%)
• Monomorphic	Monomorphic VT has a uniform and stable QRS morphology
• Polymorphic	Polymorphic VT has a continuously changing QRS morphology
• Sustained	Sustained VT: episode >30 sec in duration
• Nonsustained	Nonsustained VT: episode <30 sec in duration

(Continued on following page)

DIFFERENTIAL DIAGNOSIS OF WIDE COMPLEX TACHYCARDIA (WCT)¹ (Continued)

Arrhythmia	Characteristics
VF	Chaotic rhythm; requires advanced cardiac life support (ACLS) protocol
Torsade de pointes (TDP)	Polymorphic VT due to long QTc ≥ 460 ms
Accelerated idioventricular rhythm (AIVR)	Regular, automatic ectopic ventricular firing at rate 50-100 bpm; seen after reperfusion following acute myocardial infarction (AMI) and with digitalis toxicity
Implanted device mediated	May occur in any individual with an electronic pacemaker (see section titled pacemaker and Defibrillators)

Pearls of the History and Physical Examination

History

- Predisposing conditions
 - VT: history of angina, MI, coronary bypass, valvular disease, congestive heart failure
 - SVT: young age, previous tachyarrhythmias, WPW
 - Metabolic abnormalities, drugs (sotalol, digoxin, quinidine), muscular dystrophy, sarcoidosis, myocarditis, Chagas' disease, cocaine, inhaled glue
 - History of implantable cardiac defibrillator (ICD) or pacemaker placement
- Symptoms can range from mild (palpitations, chest pain, shortness of breath) to severe (hemodynamic compromise and shock)

Physical Examination

- Cannon A waves, fluctuations of systolic blood pressure, and variability of intensity of S₁

Diagnostic Studies and Laboratory Values

Blood Tests

- Serum tests: electrolyte abnormalities of potassium or magnesium, digoxin level, and markers of cardiac ischemia
- Urine toxicology

Electrocardiogram (ECG)

- Criteria for distinguishing VT from SVT with aberrancy
 - Determine AV dissociation^{3,4} because it is present in 60%-75% of VT but rarely seen in SVT⁵

BRUGADA CRITERIA⁶

Steps	VT	SVT with Aberrancy	Cumulative Sensitivity for VT	Cumulative Specificity for VT
Step 1: Absence of precordial lead with R-S complex?	Yes	No: go to Step 2	21%	100%
Step 2: R-S interval >100 msec in 1 precordial lead?	Yes	No: go to Step 3	66%	98%
Step 3: AV dissociation, i.e., more QRS complexes than P waves?	Yes	No: go to Step 4	82%	98%
Step 4: QRS morphology criteria in V ₁ , V ₂ , and V ₆ ?	Yes	No: SVT with aberrancy	98.7%	96.5%
RBBB-like pattern V ₁ : qR or RSR ¹	Yes			
V ₆ : R:S ratio <1				
LBBB-like pattern V ₁ : R >30 msec, R to nadir S >60 msec (verify; be specific)				
V ₆ : qR or qS				

Chest Radiograph

- Cardiomegaly or evidence of prior cardiac surgery

Echocardiography

- Identify structural heart disease

Guide to Acute Management

- Emergent unsynchronized cardioversion as per ACLS protocol in situations of hemodynamic compromise
- If hemodynamically stable VT, then determine VT or SVT with aberrancy (usually polymorphic is equivalent to VF; therefore, most likely the patient will be unstable)⁷
 - Note: may go directly to cardioversion (synchronized DCCV)
 - MVT: is ejection fraction (EF) preserved or impaired?⁷
 - Normal EF: IV procainamide or sotalol (no IV sotalol in the United States); alternatively, IV amiodarone or lidocaine may be used, although lidocaine not very effective for MVT
 - Depressed EF: amiodarone (150 mg IV bolus over 10 minutes) or lidocaine (IV 0.5-0.75 mg/kg IV push), followed by synchronized cardioversion
 - PVT: is baseline QT prolonged (TDP) or normal⁷
 - Normal QT: often ischemic; therefore, treat ischemia, correct electrolytes, and use one of the following: beta blockers, amiodarone, lidocaine, procainamide, sotalol
 - Prolonged QT (termed TDP): correct electrolytes, IV magnesium, isoproterenol, overdrive pacing, dilantin, or lidocaine
- Primary prevention after MI
 - Patient survival improved with beta blockers⁸
 - ICDs improve survival in those with history of MI, depressed left ventricular function, and inducible

VT on electrophysiology study as well as in those with $EF \leq 30\%$ ⁹

- Secondary prevention after sustained VT or cardiac arrest in those with structural heart disease: ICDs improve survival over amiodarone in survivors of cardiac arrest due to nonreversible causes
- ICDs provide better survival than amiodarone in patients with ischemic or nonischemic dilated cardiomyopathy, $EF \leq 35\%$, and New York Heart Association class II-III CHF (SCDHeFT)¹⁰



Patient Care Warnings

- VT does not necessarily result in hemodynamic compromise or collapse; thus, the presence of hemodynamic stability should not be diagnostic for SVT
- Administration of verapamil in VT may result in hypotension, VF, and death

References

- ③ 1. Braunwald E. Heart Disease, 6th ed. Philadelphia, W.B. Saunders, 2001:856-71.
- ③ 2. Aktar M, Shenasa M, Jazayeri M, et al. Wide complex tachycardia: Reappraisal of a common clinical problem. *Ann Intern Med* 1988;109:905-12.
- ③ 3. Tchou P, Young P, Mahmud R, et al. Useful clinical criteria for the diagnosis of ventricular tachycardia. *Am J Med* 1988; 84:53-56.
- ② 4. Wellens HJ, Bar FW, Lie KI. The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex. *Am J Med* 1978;64:27-33.
- ② 5. Gupta AK, Thakur RK. Wide QRS complex tachycardias. *Med Clin North Am* 2001;85:245-66.
- ① 6. Brugada P, Brugada J, Mont L, et al. A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation* 1991;83:1649-59.
- ③ 7. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2000;102:I-163.
- ① 8. A randomized trial of propranolol in patients with acute

myocardial infarction. I. Mortality results. JAMA 1982;247:1707-14.

- ① 9. Moss AJ, Hall WJ, Cannon DS, et al: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-40.
- ① 10. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med 1997;337:1576-83.

BRADYARRHYTHMIA

Definition, Etiology, and Epidemiology

- Often defined as rates less than 60 bpm, although there is no universal definition of what an abnormal lower heart rate should be
- Sinus bradycardia: P waves have normal contour
 - Patients can be symptomatic or asymptomatic
 - Marked bradycardia can be observed in asymptomatic young people or trained athletes; during sleep, rates as low as 35-40 bpm have been observed¹
 - Can occur with any increase in vagal tone or decrease in sympathetic tone (particularly medications: beta blockers, calcium channel blockers, amiodarone, lithium, clonidine)
 - Sometimes observed with meningitis, increased intracranial pressure, hypothermia, myxedema, and vomiting²
- Sick sinus syndrome: multiple sinus abnormalities including:
 - Persistent spontaneous bradycardia not caused by medications
 - Sinus arrest or sinus exit block
 - Combinations of sinus node and atrioventricular (AV) node conduction disturbances

- Tachybrady syndrome
 - In children, observed in congenital heart disease or following corrective surgery
 - In adults, observed with pathological changes in the atrial wall, including inflammation, fibrosis, and fatty infiltration^{2,3}
- First-degree AV block: 1:1 conduction with lengthened PR interval greater than 0.2 seconds
- Second-degree type I AV block (Wenckebach's period): group beating with progressive lengthening PR interval followed by a nonconducted P wave
 - Typically not associated with symptoms; does not progress to more severe conduction delays
 - Can be seen transiently in patients having an inferior myocardial infarction²
- Second-degree type II AV block: group beating, but the PR intervals remain constant, followed by a nonconducted P wave
 - Associated with conduction system disease; progression to complete AV block and syncope
 - Can be considered as a complication of anterior myocardial infarction²
- Third-degree AV block (complete heart block): no atrial-to-ventricular conduction with independent pacemaker activity
 - Seen with many atrial rates and rhythms
 - Blocks at or near the AV node are usually congenital and associated with rates of 40-60 bpm
 - Blocks at the bundle of His or below are usually acquired and associated with rates less than 40 bpm

Pearls of the History and Physical Examination

History

- Patients are usually asymptomatic
- Symptomatic bradycardia associated with symptoms

of heart failure, syncope, pre-syncope and, occasionally, palpitations or feeling of “missing a beat”

- Always take a careful medication history

Physical Examination

- Look for underlying systemic diseases (hypothyroidism, amyloidosis, or increased intracranial pressure)

Diagnostic Studies and Laboratory Values

Electrocardiogram (ECG) and Telemetry

- Diagnosis must be made by evaluation of the ECG
- Patients suspected of having bradycardia-induced syncope should be monitored on telemetry; need to establish temporal relationship of arrhythmia and symptoms; outpatient monitoring with Holter or event monitor often needed

Blood Tests

- Patients on chronic medical therapy with nodal blockers and a new arrhythmia need to have renal and hepatic function evaluated as medication metabolism can be altered

Echocardiography

- Useful when congenital, infiltrative, or structural heart disease suspected

Guide to Acute Management

- Sinus bradycardia usually does not require therapy; if associated with symptoms of low cardiac output, may give atropine 0.5 mg IV or patient may require temporary pacing (if possible, atrial

pacing preferred as it maintains ventricular synchrony)

- Sick sinus syndrome therapy is dependent on underlying physiology but usually requires permanent pacing when patients are symptomatic; often, additional medical therapy is required for control of associated tachyarrhythmias
- First-degree and second-degree type I AV block does not require any therapy⁴
- Second-degree type II AV block and complete heart block are class IIa indications of permanent pacemaker placement even when there are no associated symptoms; medication cannot be relied upon to increase the heart rate for extended periods³
- Acute medical management of bradycardia includes vagal drugs (atropine) or sympathomimetic drugs (isoproterenol)



Patient Care Warnings

- Isoproterenol should be considered only for therapy of bradycardia if myocardial infarction has been ruled out as a possible cause

References

- ③ 1. DiMarco, JP, Mangrum, JM. The evaluation and management of bradycardia. *New Engl J Med* 2000;342:703-709.
- ③ 2. Braunwald E. *Heart Disease*, 7th ed, W.B. Saunders, 2001: 797-859.
- ③ 3. Rubenstein JJ, et al. Clinical spectrum of the sick sinus syndrome. *Circulation* 1972;46:5-13.
- ③ 4. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA guidelines for implantation of cardiac pacemakers antiarrhythmia devices: A report of implantation of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). *J Am Coll Cardiol* 1998;31:1175-1209.

SYNCOPE

Definitions, Etiology, and Epidemiology

- Sudden and transient loss of consciousness (LOC) and of postural tone due to cerebral hypoperfusion, with spontaneous recovery¹
- Other causes of LOC that should be differentiated from syncope
 - Epilepsy
 - Often difficult to differentiate from syncope; cut tongue, sense of déjà vu before event, postictal period, head turning to one side support diagnosis of epilepsy²
 - No loss of postural tone in petit mal seizures
 - Sudden cardiac death: requires cardiopulmonary resuscitation or electrical/pharmacological cardioversion for recovery
 - Vertigo: associated with a sense of motion; is not syncope
 - Migraine: usually accompanies unilateral headache, scotomata, nausea
 - Somatization disorders, panic attacks, and conversion disorders: consciousness is not lost
 - Metabolic disorders
 - Hypoglycemia, hypoxia, hyperventilation
 - Differentiate based on appropriate clinical setting (history of diabetes, low oxygen saturation)
 - Usually do not cause syncope

DIFFERENTIAL DIAGNOSIS (IMPORTANT TO IDENTIFY ETIOLOGY DUE TO PROGNOSTIC IMPLICATIONS)

Cause of Syncope	Prevalence
Neurocardiogenic syncope (NCS) (reflex, neurally mediated)* • Vasovagal • Situational (cough, micturition, swallow, etc)	18%

DIFFERENTIAL DIAGNOSIS (IMPORTANT TO IDENTIFY ETIOLOGY DUE TO PROGNOSTIC IMPLICATIONS) *(Continued)*

Cause of Syncope	Prevalence
• Carotid sinus hypersensitivity (CSH) • Trigeminal neuralgia	
Orthostatic	8%
• Medications (antihypertensives, anticholinergics) • Volume depletion • Hemorrhage • Ectopic pregnancy (suspect in any reproductive-age female) • Adrenal insufficiency • Carcinoid syndrome • Dysautonomias (diabetics, multiple systems atrophy)	
Neurological†	10%
• Cerebrovascular disease (CVD) • Primary dysautonomia • Subclavian steal	
Structural cardiac or cardiopulmonary disease	4%
• Valvular disease (aortic stenosis, mitral stenosis) • Acute myocardial infarction • Anomalous coronary artery • Hypertrophic obstructive cardiomyopathy (HOCM) • Atrial myxoma • Acute aortic dissection • Pericardial tamponade • Pulmonary embolism (PE)/pulmonary hypertension	
Arrhythmias	14%
Bradyarrhythmias	
• Sinus node disease/dysfunction (SND) • 2nd- or 3rd-degree heart block • Drug-induced	
Tachyarrhythmias	
• Monomorphic ventricular tachycardia (VT) • Inherited syndromes (long QT, Brugada's) • Torsades de pointes (medications and electrolytes) • Supraventricular tachycardia (rare cause of syncope)	
Unknown*	34%

*Data pooled from studies conducted 1984-1990, before tilt table testing was commonly employed; a substantial proportion of unknown is likely neurocardiogenic in etiology³

†Neurological syncope in this report included seizures and migraines

Additional causes reported include medications (3%) and psychiatric (2%)

Adapted from Linzer et al⁴

Pearls of the History and Physical Examination

Keys to Evaluation

- Initial history, physical examination, and electrocardiogram (ECG) result yield diagnosis in 50% of all cases⁴
- Cardiac syncope should be differentiated from non-cardiac syncope due to prognostic implications; absence of evidence of heart disease excludes cardiac cause in 97% of patients¹

Cause of Syncope ⁵	Hazard Ratio for All-Cause Mortality*
Any cause	1.31 (1.14-1.51)
Cardiac	2.01 (1.48-2.73)
Unknown	1.32 (1.09-1.60)
Neurological†	1.54 (1.12-2.12)
Vasovagal or other‡	1.08 (0.88-1.34)

*Includes CVA, TIA, and seizure

†Includes vasovagal, orthostatic, and medication

‡Multivariable adjusted

Adapted from Soteriades et al⁵

- Neurological testing is rarely helpful unless neurological signs are present⁴
- Polypharmacy often leads to syncope in elderly

History

- Focus on defining: syncope versus nonsyncope; cardiac versus noncardiac etiology¹
- Activity before event: posture, activity/exertion, association with situations, neck motion, prolonged standing
- Symptoms before event: nausea/vomiting, diaphoresis, aura, abdominal pain, chest pain, palpitations
- Symptoms after event: nausea/vomiting, diaphoresis, bowel/bladder incontinence, skin color, injury

- If witness present: question about whether true syncope occurred, duration of event, and movements during event
- Past history of heart problems, metabolic disorders, medication use (QT prolongation), previous syncope
- Medications: antihypertensives, anticholinergics, QT prolonging agents
- Family history of sudden death, congenital heart disease

SYMPTOMS SUGGESTIVE OF ETIOLOGY OF LOC

Symptoms	Etiology
Palpitations, chest pain, or associated with exertion	Cardiac syncope
Associated with exertion	Aortic stenosis, cardiac syncope
After unpleasant sight, sound, smell	Neurocardiogenic
Prolonged standing	Neurocardiogenic
Nausea, vomiting, abdominal pain, diaphoresis before or after event	Neurocardiogenic
During urination, defecation, coughing, swallowing	Neurocardiogenic
Facial pain	Trigeminal neuralgia
Head rotation, shaving, tight collar	Carotid sinus hypersensitivity
Supine → standing position	Orthostatic
Vertigo, dysarthria, diplopia	Brainstem transient ischemic attack (TIA)
Arm exercise	Subclavian steal
Confusion after attack or LOC >5 minutes*	Seizure
Aura	Seizure
Frequent syncope, somatic complaints, no heart disease	Psychiatric cause

*May rarely be seen in aortic stenosis

Physical Examination

- Orthostatic changes, differing BP in extremities (aortic dissection, subclavian steal), carotid sinus massage (CSM) (see below), murmur, gallop, bruits, jugular venous pressure, neurological examination, injury

Diagnostic Studies and Laboratory Values

ECG

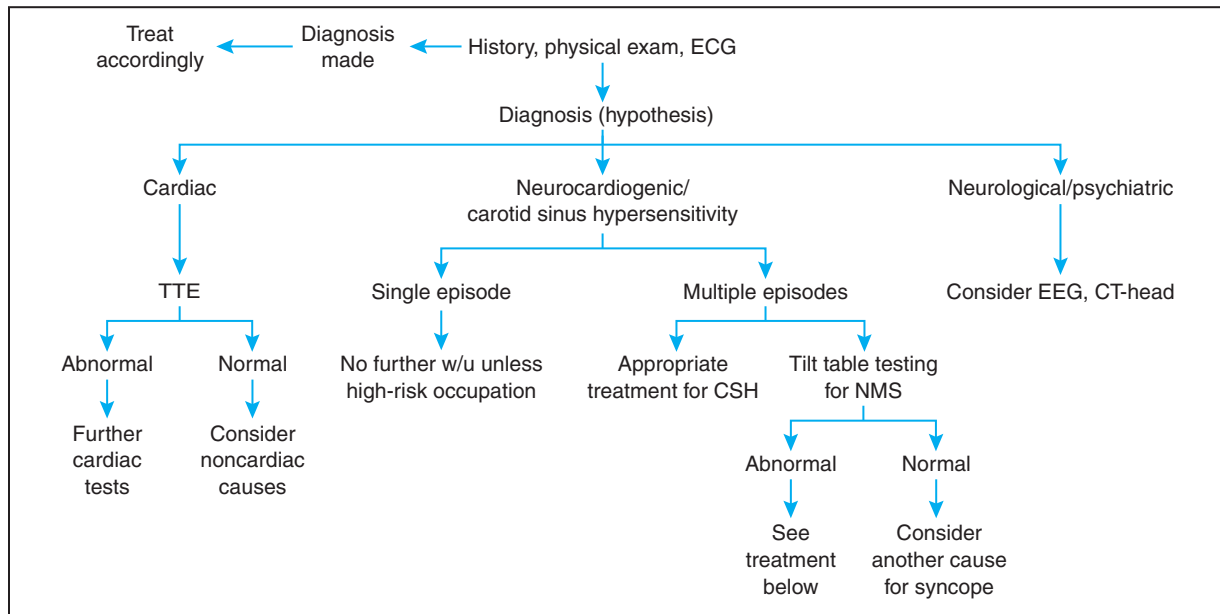
- Diagnosis of arrhythmia is rare but can provide diagnostic clues
- Following are abnormal and raise concern for a cardiac cause of syncope: bifascicular block, prolonged QRS, sinus bradycardia ($<50/\text{min}$), prolonged QT, evidence of Brugada's syndrome or WPW, preexcited QRS, Q waves, evidence of active ischemia, bundle branch block (BBB) (may suggest paroxysmal atrioventricular block [AVB]), and left ventricular hypertrophy suggestive of hypertrophic cardiomyopathy¹

Blood Tests

- If metabolic cause or decreased circulating volume suspected (class I)
- Serum chemistries: electrolytes, glucose, hemoglobin/hematocrit levels, oxygen saturation

Guide to Acute Management

- All patients with suspected cardiac cause of syncope should be placed on continuous telemetry monitoring and undergo transthoracic echocardiogram (TTE) to evaluate function and structural abnormalities
- Ruling out myocardial infarction should be considered in any patient suspected of having cardiac syncope



Algorithm for LOC without known etiology. (Adapted from Ammirati F, Colivicchi F, Santini M. Diagnosing syncope in clinical practice: Implementation of a simplified diagnostic algorithm in a multicentre prospective trial. The OESIL 2 Study [Osservatorio Epidemiologico della Sincope nel Lazio]. Eur Heart J 2000;21:935-40.)

Hospitalization Recommendations¹

- Known significant heart disease
- ECG abnormalities as described
- Syncope with exercise
- Family history of sudden death
- Consider for palpitations, syncope in supine position
- For treatment of underlying cause (CVA, PE, aortic dissection, etc.)
- Recurrent hospitalizations for diagnosis rarely productive⁷

Diagnosis-Specific Management

Neurocardiogenic

- Unclear mechanism, one theory: Upright position → ↓venous return to heart → ↓ systemic arterial pressure → reflex tachycardia and peripheral vasoconstriction? cardiac mechanoreceptors activated → ↓ sympathetic output and → vagal tone ↑ vasodilation and cardiac inhibition⁸
- No workup for single episode unless occupational risk (pilots, bus drivers, etc.)
- Diagnosis: tilt table
 - Class I indications: for single episode, high-risk occupation, or recurrent unexplained episodes¹; not recommended if diagnosis would not alter therapy or to assess efficacy of therapy (class III)^{9,10}
 - Tilt to 60° for 45 minutes: if negative, repeating with either isoproterenol or sublingual nitroglycerin, thus increasing sensitivity but decreasing specificity
 - Positive test: syncope during test (class I)¹; negative test does not rule out neurocardiogenic etiology¹¹
- Treatment

- Avoid trigger events and discontinue offending medications (class I)
- Maneuvers: leg crossing, muscle tensing^{12,13}
- Pacemaker, if cardioinhibitory response present during tilt-table testing, >5 attacks per year or age >40 years and severe injury with episodes (class IIa); not recommended in the absence of symptoms on tilt test (class III)¹⁴
- Sodium supplements (class II)
- Tilt training (class II)
- Beta blockers not recommended (class III)^{15,16}
- Selective serotonin reuptake inhibitors have proved effective in small trials¹⁷

Carotid Sinus Hypersensitivity

- Diagnosis: CSM (class I) in those >40 years old and without carotid bruits¹
 - Diagnosed with continuous ECG monitoring
 - Massage carotid for 5 seconds at level of cricoid cartilage with patient in supine position; repeat in 1-2 minutes on opposite carotid, and then repeat with patient in erect position
 - Positive test result: reproduction of symptoms in addition to either ventricular pause >3 seconds (cardioinhibitory) or systolic blood pressure (SBP) ↓ >50 mm Hg¹
- Treatment
 - Pacemaker if cardioinhibitory response during CSM (class I)¹⁴
 - Other modalities less well proven: fludrocortisone, leg crossing, squatting, abdominal/waist-height support stockings

Cerebrovascular Accident/TVA

- Unlikely cause of syncope without other focal neurological deficits

- In vertebrobasilar insufficiency, usually vertigo, ocular-movement disorders, dysarthria, tinnitus, and paralysis usually predominate
- In anterior circulation disease, focal neurological impairment predominates
- Routine CT-head, EEG not warranted unless other deficits present

Orthostasis (decrease of SBP ≥ 20 mm Hg 3 minutes after supine position)¹

- Treat underlying cause if possible
- Treatment for idiopathic orthostatic hypotension: avoid alcohol, rise slowly, dorsiflexion of feet before standing, alpha agonist midodrine, Jobst stockings

Syncope Due to Cardiac Structural Disease

- Transthoracic echocardiogram: diagnostic yield low (diagnosis only of valvular disease and structural abnormalities); however, low ejection fraction may be used to identify those at increased risk for having arrhythmic etiology (class D)

Syncope Due to Cardiac Arrhythmia

- ECG monitoring: class I indication if unexplained syncope where cause is not obvious¹⁵
 - Holter: not the test of choice unless symptoms frequent (>1 episode/day)
 - Looping event monitor when bradyarrhythmia suspected or symptoms less frequent
 - Insertable looping monitor (REVEAL, Medtronic Inc.) may increase diagnostic yield¹⁸
 - Diagnosis
 - Confirmed when correlations between symptoms and ECG abnormalities (class I)¹
 - Excludes arrhythmia when syncope occurs with sinus rhythm (class I)
- Electrophysiology study

- Indications
 - Consider for abnormal ECG, structural heart disease, or palpitations (class I)¹⁹
 - Symptomatic patients with suspected sinus node dysfunction (class I)¹⁹
 - Not indicated with known patients with known association of symptoms and sinus node dysfunction (SND), AVB, or BBB (class III)¹⁹
- Diagnosis
 - Inducible VT where syncope associated with increased risk of death²⁰
 - Polymorphic VT and ventricular fibrillation are nonspecific findings (class II)
 - Normal electrophysiology study (EPS) does not rule out arrhythmic cause for syncope²¹; however, patients with normal EPS have favorable outcomes²²; if concern for arrhythmia still exists, consider long-term ECG monitoring
- Exercise testing (ETT)
 - Indications
 - Consider when syncope occurs during exertion (class I)¹
 - Perform transthoracic echocardiogram before ETT
 - Diagnosis
 - Positive when syncope occurs with the presence of hemodynamic and ECG abnormalities (class I)
 - Also positive in absence of syncope if Mobitz type II or III discovered (class I)

Arrhythmia-Specific Management

Monomorphic Ventricular Tachycardia

- Prognosis poor in setting of ischemic cardiomyopathy (coronary artery disease [CAD]) with low ejection fraction (EF)
- If syncope occurs in the setting of low EF and history of CAD, refer for EPS to screen for inducible

VT, in which case an implantable cardiac defibrillator (ICD) is warranted²³

- Syncope in the setting of low EF in nonischemic cardiomyopathy may warrant ICD²⁴
- If EPS negative, consider outpatient ECG monitoring (see the section on ECG monitoring)

Sinus Node Dysfunction (SND)

- Pacemaker placement for sinus pauses correlating with symptoms (class I), unexplained syncope, and SND during EPS (class IIa)¹⁴

Atrioventricular Block

- Pacemaker placement for type II second degree, third degree, or any symptomatic AVB (class I)¹⁴

Brugada's Syndrome and Long QT Syndrome

- Consider for syncope with positive family history and without alternative diagnosis (class II)

Polymorphic VT (torsade de pointes) (see section titled Wide Complex Tachycardia)

- Drug-induced¹: remove offending agent, temporary pacing, IV magnesium
- Electrolytes (low magnesium, potassium, calcium): replete
- Congenital: ICD placement

Driving Instructions¹

- Restrict from driving if cardiac syncope suspected
- NCS: no restrictions if not high-risk occupation, in which case restrict until symptoms controlled
- In syncope of uncertain cause, restrict for 3 months or until specialist evaluation in high-risk occupations



Patient Care Warnings

- Cardiac syncope must be excluded in patients with low ejection fraction or structural heart disease
- Telemetry monitoring should be performed for all patients with suspected cardiac syncope
- Protocol for ruling out myocardial infarction should also be strongly considered in patients suspected of having cardiac syncope
- Convulsions are not specific for seizures
- Ventricular fibrillation is associated with cardiac arrest and not cardiac syncope
- Neurological testing is rarely helpful, unless other neurological symptoms are present

References

- ③ 1. Brignole M, Alboni P, Benditt D, et al. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J* 2001; 22:1256-1306.
- ① 2. Sheldon R, Rose S, Ritchie D, et al. Historical criteria that distinguish syncope from seizures. *J Am Coll Cardiol* 2002;40: 142-48.
- ② 3. Mathias CJ, Deguchi K, Schatz I. Observations on recurrent syncope and presyncope in 641 patients. *Lancet* 2001;357: 348-53.
- ③ 4. Linzer M, Yang EH, Estes NA, et al. Diagnosing syncope: Value of history, physical examination, and electrocardiography. Clinical Efficacy Assessment Project of the American College of Physicians. *Ann Intern Med* 1997; 126:989-96.
- ② 5. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med*. 2002;347:878-85.
- ① 6. Ammirati F, Colivicchi F, Santini M. Diagnosing syncope in clinical practice: Implementation of a simplified diagnostic algorithm in a multicentre prospective trial. The OESIL 2 Study (Osservatorio Epidemiologico della Sincope nel Lazio). *Eur Heart J* 2000;21:935-40.
- ③ 7. Lipsitz LA. Syncope in the elderly. *Ann Intern Med* 1983;99: 92-105.

- ③ 8. Mosqueda-Garcia R, Furlan R, Tank J, et al. The elusive pathophysiology of neurally mediated syncope. *Circulation* 2000;102:2898-906.
- ① 9. Shen WK, Jahangir A, Beinborn D, et al. Utility of a single-stage isoproterenol tilt table test in adults: A randomized comparison with passive head-up tilt. *J Am Coll Cardiol* 1999;33:985-90.
- ① 10. Raviele A, Giada F, Brignole M, et al. Comparison of diagnostic accuracy of sublingual nitroglycerin test and low-dose isoproterenol test in patients with unexplained syncope. *Am J Cardiol* 2000;85:1194-98.
- ② 11. Moya A, Brignole M, Menozzi C, et al. Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. *Circulation* 2001;104:1261-67.
- ① 12. Brignole M, Croci F, Menozzi C, et al. Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. *J Am Coll Cardiol* 2002;40:2053-59.
- ① 13. Krediet CT, van Dijk N, Linzer M, et al. Management of vasovagal syncope: Controlling or aborting faints by leg crossing and muscle tensing. *Circulation* 2002;106:1684-89.
- ③ 14. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *Circulation* 2002;106:2145-61.
- ① 15. Flevari P, Livanis EG, Theodorakis GN, et al. Vasovagal syncope: A prospective, randomized, crossover evaluation of the effect of propranolol, nadolol and placebo on syncope recurrence and patients' well-being. *J Am Coll Cardiol* 2002;40:499-504.
- ① 16. Madrid AH, Ortega J, Rebollo JG, et al. Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population: A prospective, double-blind, randomized and placebo-controlled study. *J Am Coll Cardiol* 2001;37:554-59.
- ① 17. Di Girolamo E, Di Iorio C, Sabatini P, et al. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: A randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1999;33:1227-30.
- ② 18. Krahm AD, Klein GJ, Fitzpatrick A, et al. Predicting the outcome of patients with unexplained syncope undergoing prolonged monitoring. *Pacing Clin Electrophysiol* 2002;25:37-41.
- ③ 19. Zipes DP, DiMarco JP, Gillette PC, et al. Guidelines for clinical intracardiac electrophysiological and catheter ablation procedures. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Intracardiac Electrophysiologic and Catheter Ablation Procedures), Developed in Collaboration with the North American Society of Pacing and Electrophysiology. *J Am Coll Cardiol* 1995;26:555-73.

- ① 20. Olshansky B, Hahn EA, Hartz VL, et al. Clinical significance of syncope in the electrophysiologic study versus electrocardiographic monitoring (ESVEM) trial. The ESVEM Investigators. *Am Heart J* 1999;137:878-86.
- ② 21. Link MS, Kim KM, Homoud MK, et al. Long-term outcome of patients with syncope associated with coronary artery disease and a nondiagnostic electrophysiologic evaluation. *Am J Cardiol* 1999;83:1334-47.
- ① 22. Menozzi C, Brignole M, Garcia-Civera R, et al. Mechanism of syncope in patients with heart disease and negative electrophysiologic test. *Circulation* 2002;105:2741-45.
- ① 23. Pires LA, May LM, Ravi S, et al. Comparison of event rates and survival in patients with unexplained syncope without documented ventricular tachyarrhythmias versus patients with documented sustained ventricular tachyarrhythmias both treated with implantable cardioverter-defibrillators. *Am J Cardiol* 2000;85:725-28.
- ① 24. Knight BP, Goyal R, Pelosi F, et al. Outcome of patients with nonischemic dilated cardiomyopathy and unexplained syncope treated with an implantable defibrillator. *J Am Coll Cardiol*. 1999;33:1964-70.

AORTIC STENOSIS AND REGURGITATION

Definition, Etiology, and Epidemiology

Aortic Stenosis

- Decrease in the area of the aortic valve from degeneration and calcification of aortic leaflets
- Obstructs left ventricular outflow and increases pressure load, leading to left ventricular hypertrophy
- A very common valve lesion in the United States¹

ETIOLOGY¹⁻⁴

Type	Comment
Calcific	Presents in sixth or seventh decade with tricuspid valve; earlier with bicuspid; almost half of cases in patients older than 70 years are calcific ² ; more rapid progression with renal insufficiency

(Continued on following page)

ETIOLOGY¹⁻⁴ (Continued)

Type	Comment
Congenital	1%-2% of population born with bicuspid valve; present with stenosis in fourth or fifth decade (50% of cases in patients younger than 70 years due to bicuspid valve) ²
Rheumatic heart disease	Unusual to have aortic valve involvement without mitral valve disease
Obstructive infective vegetations	

Aortic Regurgitation

- Results from disease of either the aortic leaflets or the aortic root distorting the leaflets to prevent their coaptation
- Regurgitant blood causes volume overload in the left ventricle; initially, this is compensated with hypertrophy and increased contractility but can eventually lead to left ventricular dilation and failure
- Acute aortic insufficiency much less well tolerated as compensatory mechanisms do not have time to develop

ETIOLOGY¹⁻⁴

Acute Aortic Insufficiency	Chronic Aortic Insufficiency
Infective endocarditis	Rheumatic heart disease
Aortic dissection involving valvular apparatus	Hypertension with aortic root dilation
Trauma to chest wall	Bicuspid valve
	Syphilitic aortitis
	Subacute infective endocarditis
	Marfan's syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta (disorders of collagen production)
	Ankylosing spondylitis, Reiter's syndrome, psoriasis (HLA-B27 linked)

Pearls of the History and Physical Examination

Aortic Stenosis

- Cardinal symptoms are angina (35%), syncope (often exertional) (15%), and heart failure (due to diastolic or systolic dysfunction) (50%)⁵
- May present with sudden cardiac death
- History of predisposing conditions above or renal insufficiency
- Important to distinguish between aortic stenosis and left ventricular outflow obstruction i.e. hypertrophic cardiomyopathy

Aortic Regurgitation

- Consider predisposing or historical facts noted previously
- Symptoms depend on the rapidity with which the regurgitation develops
- Acute aortic regurgitation: abrupt onset dyspnea, orthopnea, and paroxysmal nocturnal dyspnea
- Chronic aortic regurgitation: gradually progressive symptoms of heart failure, hepatomegaly, ascites
- Fever with infective endocarditis
- Hypertension with chest and back pain in aortic dissection

Physical Finding	Aortic Stenosis	Aortic Regurgitation
Pulses	Carotid pulses delayed and diminished in amplitude (parvus et tardus)	Widened pulse pressure; bounding pulses (water hammer); visible capillary pulsations in nail beds (Quincke’s pulse)
Palpation	Heaving point of maximal impulse with delay between apical impulse and carotid pulse, systolic thrill over aortic area	Forceful apical impulse that may be displaced

(Continued on following page)

Physical Finding	Aortic Stenosis	Aortic Regurgitation
Heart sounds	Normal S_1 , diminished S_2 , S_4	Diminished S_2 , S_3
Murmurs	Harsh crescendo-decrescendo systolic murmur at second right intercostal space	Blowing decrescendo diastolic murmur at left sternal border
Radiation	Carotid arteries, subclavian arteries, apex mimicking mitral regurgitation (Gallivardin's phenomenon)	To apex; aortic jet impinging on mitral valve leaflet mimicking mitral stenosis (Austin Flint murmur)
Eponyms (miscellaneous)	More severe stenosis with: 1. Greater delay in pulse 2. Later peak of murmur in systole 3. Loss of physiological split of S_2 (delayed A_2)	de Musset's sign: head bobbing Müller's sign: pulsations of uvula Traube's sound: double sound at compressed femoral artery Hill's sign: systolic blood pressure in leg exceeding that in arm by at least 30 mm Hg

Diagnostic Studies and Laboratory Values

Aortic Stenosis

- Chest x-ray: normal or enlarged cardiomedial silhouette; calcified aorta
- Electrocardiography (ECG): Evidence of left ventricular hypertrophy
- Echocardiography: shows thickened aortic valve with decreased movement
 - Furthermore, valve area and gradient can be estimated using Doppler flow
 - Mild AS valve area $>1.5 \text{ cm}^2$; moderate AS valve area $>1.0\text{--}1.5 \text{ cm}^2$; severe AS valve area $\leq 1.0 \text{ cm}^2$ (see⁵)

Aortic Regurgitation

- Chest x-ray: enlarged cardiomeastinal silhouette with left ventricular prominence
- ECG: Left ventricular hypertrophy
- Echocardiography: assessment of aortic valve area, ejection fraction, end systolic/diastolic volumes, degree and velocity of regurgitant flow

Guide to Acute Management

Aortic Stenosis

- No effective medical management for symptomatic aortic stenosis^{6,7}
- Surgical aortic valve replacement has shown to improve survival significantly
- When aortic stenosis used for symptom control, be careful with vasodilating antihypertensives and diuretics, which can decrease afterload and preload (respectively) excessively, leading to decreased cardiac output

PROGNOSIS WITHOUT SURGICAL CORRECTION²

Presenting Symptom	Average Survival
Angina	5 years
Syncope	3 years
Left ventricular dysfunction	2 years

Acute Aortic Regurgitation

- Acute aortic regurgitation is poorly tolerated; use of vasodilators and diuretics should be prompt with evidence of left ventricular failure; nitroprusside is a good choice due to ease of titration³
- Low threshold for surgical intervention with aortic valve replacement if medical therapy fails

Chronic Aortic Regurgitation (AR)

- Vasodilators are mainstay of therapy for nonsurgical AR to improve forward output and decrease regurgitant volume. reduction in left ventricular (LV) end-diastolic volume and preservation of ejection fraction have been noted with hydralazine, angiotensin-converting enzyme inhibitors, and nifedipine⁸
- Diuretics for symptoms of volume overload
- Indications for aortic valve replacement⁸
 - Symptoms attributed to severe AR
 - Asymptomatic with LV end-systolic dimension nearing 55 mm
 - Asymptomatic with LV end-systolic volume approaching 55 mL/m²
 - Asymptomatic with LV ejection fraction <55%



Patient Care Warnings

- Careful with antihypertensives and diuretics in patients with aortic stenosis
- Acute aortic regurgitation is poorly tolerated; consider early surgical intervention if possible

References

- ③ 1. Carabello B. Valvular heart disease. *N Eng J Med* 1997;337:32-41.
- ③ 2. Braunwald E. *Heart Disease*, 6th ed. W.B. Saunders, Philadelphia, 2001:1671-88.
- ③ 3. Hillis LD, Lange RA, et al. *Manual of Clinical Problems in Cardiology*, 6th ed. Lippincott, Philadelphia, 2003:337-49.
- ③ 4. Harris KM, Robiolio P. Valvular heart disease. *Postgrad Med* 1999;106:113-28.
- ③ 5. Bonow RO, Carabello B, et al. Guidelines for the management of patients with valvular disease: Executive summary. *Circulation* 1998; 98:1949-84.
- ③ 6. Carabello B. Aortic stenosis. *N Eng J Med* 2002;346:677-82.
- ③ 7. Boon NA, Bloomfield P. Medical management of valvular heart disease. *Heart* 2002;87:395-400.
- ③ 8. Grayburn PA. Vasodilator therapy for chronic aortic and mitral regurgitation. *Am J Med Sci* 2000;320:202-08.

MITRAL STENOSIS AND REGURGITATION

Definition, Etiology, and Epidemiology

Mitral Stenosis

- Rigidity or immobility of mitral valve leaflets leading to impaired opening during diastole
- Normal valve area 4-6 cm²; symptoms may develop at a valve area of approximately 1.5-2 cm² where a left atrial-left ventricle (LA-LV) pressure gradient develops to maintain cardiac output^{1,2}
- Flow of blood from the left atrium to the left ventricle is impaired, leading to increased left atrial pressures; further increase in pressure with volume overload or tachycardia where diastole is shortened and left ventricular filling is impaired

ETIOLOGY¹⁻³

Type	Comment
Rheumatic	Accounts for majority of cases, although history of rheumatic fever may be obtained in only 50%-70% of patients ²
Infective endocarditis	
Mitral annular calcification	
Congenital malformation, systemic lupus erythematosus, carcinoid, endomyocardial fibrosis	<1% of cases combined

Mitral Regurgitation

- Coaptation failure of the mitral valve leaflets due to any disorder that affects one or more components of the mitral valve apparatus; includes the annulus, chordae tendinae, and papillary muscles or leaflets
- During systole, blood ejected into left atrium, causing increased volume load on the left ventricle

- In most patients, compensation occurs via more complete emptying of the left ventricle and eccentric cardiac hypertrophy; however, symptoms of heart failure become prominent as the chronic volume overload leads to left ventricular failure

ETIOLOGY^{1,3,4}

Type	Comment
Acute mitral regurgitation	
Infective endocarditis	Usually with highly virulent organisms such as <i>Staphylococcus aureus</i> / <i>Streptococcus pneumoniae</i> and caused by rupture of infected chordae or perforation of valve
Rupture of chordae tendinae	Myxomatous degeneration, trauma, infective endocarditis (not associated with ischemia)
Rupture or dysfunction of papillary muscle	Typically in setting of ischemia of LV and papillary muscle; infiltrative disorders
Chronic mitral regurgitation	
Myxomatous degeneration of the valve	
Mitral valve prolapse	Most common cause in surgical series
Rheumatic	Usually with some component of valve stenosis
Functional	As a result of LV dysfunction and dilation of annulus

Pearls of the History and Physical Examination^{2,3}

Mitral Stenosis

- Attempt to elicit history of rheumatic fever, although this is often difficult as symptoms develop 15-20 years after rheumatic injury
- Classic symptoms of dyspnea, orthopnea, and paroxysmal dyspnea as LA pressures increase
- Hemoptysis
- Palpitations with concurrent atrial fibrillation
- Symptoms often appear in young females during

pregnancy or when patient has increased circulatory volume

Mitral Regurgitation

- Symptoms are heart failure or arrhythmia secondary to enlarged left atrium
- Rapidity of symptoms and setting in which they occur can help elicit diagnosis
- Acute mitral regurgitation
 - Abrupt onset dyspnea, orthopnea, and paroxysmal nocturnal dyspnea with evidence of acute pulmonary edema
 - History of recent myocardial infarction (MI) (inferior wall MI more common than anterior wall MI)
 - Symptoms consistent with infective endocarditis
- Chronic mitral regurgitation
 - Symptoms of heart failure are gradual
 - History of rheumatic fever

Physical Finding	Mitral Stenosis	Mitral Regurgitation
Palpation and inspection	Mid-diastolic thrill over apex; jugular venous distention	Jugular venous distention; laterally displaced point of maximal impulse; systolic thrill or S_3 palpated at apex
Heart Sounds	Loud S_1 ; S_2 followed by opening snap heard at left sternal border	Diminished intensity of S_1 ; S_3 may also be heard
Murmurs	Low-pitched diastolic rumble after the opening snap at apex (best heard with patient in left lateral decubitus position)	Blowing holosystolic murmur at apex with radiation to axilla
Miscellaneous	Severity of mitral stenosis may be graded by time from A_2 to opening snap, with shorter interval suggesting more severe stenosis	Presence of S_3 suggests more severe mitral regurgitation

Diagnostic Studies and Laboratory Values

Mitral Stenosis

- Chest x-ray: enlarged left atrium or LA appendage, which may be represented by straight left heart border
- Electrocardiogram: atrial fibrillation in many cases; evidence of LA enlargement (broad biphasic P wave in V₁) if in sinus rhythm
- Echocardiography: quantification of mitral stenosis and LA size and for evidence of pulmonary artery hypertension

Severity	Valve Area
Mild	1.6-2.0 cm ²
Moderate	1.1-1.5 cm ²
Severe	<1.0 cm ²

Adapted from references 3 and 5

Mitral Regurgitation

- Chest x-ray: enlarged left atrium and left ventricle with evidence of pulmonary vascular redistribution
- Electrocardiogram: LA enlargement and LV hypertrophy
- Echocardiography: may reveal flail mitral leaflet, mitral valve prolapse, vegetations or ruptured papillary muscle or chordae tendinae
- Pulmonary artery catheter: elevated pulmonary capillary wedge pressure with large regurgitant *v*-wave

Guide to Acute Management

Mitral Stenosis

- Only therapy indicated for asymptomatic mitral stenosis is endocarditis prophylaxis⁵
- Diuresis for symptomatic patients

- Rate-controlling agents if atrial fibrillation is present
- Anticoagulation⁵
 - Patients with atrial fibrillation (American College of Cardiology/American Heart Association class I recommendation)
 - Prior history of embolism with or without atrial fibrillation (class I)
 - Consider in patients with LA dimension ≥ 55 mm by echo (class II)
- Symptomatic patients should be considered for mitral valve surgery or balloon valvuloplasty

Mitral Regurgitation

- Chronic mitral regurgitation
 - Functional mitral regurgitation due to annular dilation from dilated cardiomyopathy should be treated with standard therapy for heart failure (afterload reduction to improve forward cardiac output)
 - Vasodilator therapy with angiotensin-converting enzyme inhibitors and nifedipine has shown reduction in symptoms and regurgitant volume, however, the greatest benefit is seen in those with poor systolic function and annular dilation⁶⁻⁸
 - Indications for surgery^{5,7}
 - Symptomatic mitral regurgitation with New York Heart Association class II symptoms or worse, even with preserved EF ($>60\%$) or LV end-systolic dimension <45 mm
 - Asymptomatic with LV end-systolic dimension approaching 45 mm
 - Asymptomatic patients with EF $<60\%$
- Acute mitral regurgitation
 - Tolerated poorly from hemodynamic standpoint and often requires immediate surgical correction
 - Nitroprusside, if tolerated, to improve flow to systemic circulation via afterload reduction

- Dobutamine or dopamine may be required to maintain cardiac output
- Consider intra-aortic balloon counterpulsation (IABP) as bridge to surgical correction



Patient Care Warnings

- Acute mitral regurgitation is poorly tolerated, and mortality is high without surgical intervention; consider inotropes or IABP early as bridge to surgery
- Consider mitral stenosis in young patients (females > males) with signs/symptoms of pulmonary edema and/or atrial fibrillation
- Patients with mitral stenosis tolerate increased circulatory volume and tachycardia poorly; be careful with fluids

References

- ③ 1. Carabello BA, Crawford FA Jr. Valvular heart disease. *N Engl J Med* 1997;337:32-41.
- ③ 2. Braunwald E. *Heart Disease*, 6th ed. WB Saunders, 2001: 1643-65.
- ③ 3. Hillis LD, Lange RA, et al. *Manual of Clinical Problems in Cardiology*, 6th ed. Lippincott, 2003:356-68.
- ③ 4. Harris KM, Robiolio P. Valvular heart disease. *Postgrad Med* 1999;106:113-28.
- ③ 5. Bonow RO, Carabello B, et al. Guidelines for the management of patients with valvular disease: Executive summary. *Circulation* 1998;98:1949-84.
- ③ 6. Boon NA, Bloomfield P. Medical management of valvular heart disease. *Heart* 2002;87:395-400.
- ③ 7. Grayburn PA. Vasodilator therapy for chronic aortic and mitral regurgitation. *Am J Med Sci* 2000;320:202-8.
- ③ 8. Levine HJ, Gaasch WH. Vasoactive drugs in chronic regurgitant lesions of the mitral and aortic valves. *J Am Coll Cardiol* 1996;28:1083-91.

TRICUSPID STENOSIS AND REGURGITATION

Definition, Etiology, and Epidemiology

Tricuspid Stenosis

- Obstruction of flow from right atrium (RA) to right ventricle (RV), usually due to leaflet fusion
- Normal tricuspid valve area is decreased, leading to symptoms at a pressure gradient of only 3-5 mm Hg between RA and RV (due to low pressures on right side of heart)^{1,2}

ETIOLOGY^{2,3}

Type	Comment
Rheumatic heart disease	Most common cause, but very unusual without left-sided involvement; 15%-20% of rheumatic heart involvement at autopsy, but only 5% become clinically significant ^{1,2}
Congenital	
Carcinoid heart disease	Unusual without tricuspid regurgitation
Right atrial masses	Cardiac myxoma, noncardiac metastases, thrombus
Pacemaker or defibrillator leads	

Tricuspid Regurgitation

- Failure of coaptation of the tricuspid valves leads to regurgitant flow from RV to RA
- Most commonly functional rather than organic in origin, with the former secondary to RV (and annular) dilation

ETIOLOGY¹⁻³

Type	Comment
<i>Chronic Tricuspid Regurgitation</i>	
Dilated cardiomyopathy (functional)	Tricuspid valve leaflets typically normal in structure
Pulmonary hypertension	Secondary to left-sided systolic dysfunction; congenital heart disease, primary or secondary pulmonary hypertension leading to RV dilation
Rheumatic heart disease	Typically with some component of stenosis
Carcinoid heart disease	Deposition of fibrous plaques on ventricular surface of leaflets
<i>Infective Endocarditis</i>	
Ebstein's anomaly	Spectrum of tricuspid valve abnormalities, including leaflet dysplasia and displacement, absent chordae, and abnormal papillary muscles
Drug-induced	Use of phentermine-fenfluramine combination as weight-loss formula
Systemic lupus erythematosus	
<i>Acute Tricuspid Regurgitation</i>	
Infective endocarditis	More common in intravenous drug users (50% of native tricuspid valve endocarditis compared with 9%-15% in nonintravenous drug abusers) ³
RV infarction with papillary muscle dysfunction	
Ruptured chordae tendinae	

Pearls of the History and Physical Examination

Tricuspid Stenosis

- Elicit history of rheumatic fever, although this is often difficult as symptoms develop 15-20 years after rheumatic injury

- Symptoms of reduced exercise tolerance due to decreased cardiac output, abdominal fullness, increased abdominal girth (ascites), and peripheral edema; these symptoms are typically out of proportion to classic symptoms of left ventricular dysfunction (orthopnea and paroxysmal nocturnal dyspnea)

Tricuspid Regurgitation

- In the absence of pulmonary hypertension, tricuspid regurgitation is well tolerated
- With concurrent pulmonary hypertension, symptoms of abdominal fullness, RUQ pain, jaundice, lower extremity swelling

Physical Finding	Tricuspid Stenosis	Tricuspid Regurgitation
Palpation and inspection	Elevated jugular venous pressure (JVP) with large <i>a</i> wave, icteric skin, enlarged liver, ascites	Elevated JVP with prominent regurgitant <i>v</i> wave; parasternal heave; enlarged pulsatile liver
Heart sounds	Increased intensity of S_1	Diminished S_1 ; loud P_2 if pulmonary hypertension present
Murmurs	Rumbling mid-diastolic murmur at right heart border increasing in intensity with inspiration	Blowing holosystolic murmur at left sternal border increasing with inspiration
Miscellaneous	Increase in intensity of murmur with inspiration is called Carvallo's sign	Murmur may not be present with massive tricuspid regurgitation or severe RV failure

Diagnostic Studies and Laboratory Values

Tricuspid Stenosis

- Chest x-ray: RA enlargement suggested by prominence of right heart and engorgement of superior

vena cava and azygos vein without dilation of the pulmonary artery; pulmonary venous congestion with concurrent mitral valve disease

- Electrocardiogram: evidence of RA enlargement with tall P waves in lead II; absence of voltage criteria for right ventricular hypertrophy may distinguish tricuspid stenosis from other causes of RA enlargement
- Echocardiography: thickened tricuspid valve with decreased excursion; enlarged RA; increased forward flow velocities and gradient across tricuspid valve

Tricuspid Regurgitation

- Chest x-ray: RV and RA enlargement; prominent azygos vein without pulmonary congestion
- Electrocardiogram: right axis deviation possibly with RV hypertrophy; also evidence of RA enlargement by peaked P wave in lead II; atrial fibrillation may be present, which does not allow assessment of P-wave morphology
- Echocardiography: assesses valves and presence of vegetation or anomaly
- Pulmonary artery catheter: RA pressure tracing often shows loss of the x descent and prominent v waves
- Laboratory tests: leukocytosis and blood cultures with infective endocarditis

Guide to Acute Management

Tricuspid Stenosis

- Diuretics and salt restriction for symptoms of volume overload
- Surgical intervention or balloon valvuloplasty should be considered if there is evidence of low cardiac output

Tricuspid Regurgitation

- Usually secondary to RV dilation (functional) and improves with diuresis and decreases in volume of RV; if pulmonary hypertension is secondary to other underlying etiology, i.e., mitral stenosis, then significant improvement is seen with correction of primary cause
- Aggressive diuresis is often required to improve right-sided volume
- Resolution of infective endocarditis with appropriate antibiotics may prevent need for valve replacement (see section titled Infective Endocarditis)

References

- ③ 1. Braunwald E. Heart Disease, 6th ed. WB Saunders, 2001: 1689-94.
- ③ 2. Hillis LD, Lange RA, et al. Manual of Clinical Problems in Cardiology, 6th ed. Lippincott, 2003:382-87.
- ③ 3. Raman S, et al. Tricuspid valve disease: Tricuspid valve complex perspective. Curr Prob Cardiol 2002;27:97-144.

INDICATIONS FOR EMERGENT ECHOCARDIOGRAPHY

Echocardiographic Findings of Pericardial Tamponade^{1,2}

- Pericardial tamponade is a clinical diagnosis; a transthoracic echocardiogram (TTE) can be performed to confirm the presence and location of a pericardial effusion; clinical acuity of effusion depends on the time it takes to develop (see section titled Pericardial Effusion and Cardiac Tamponade)
- Abnormal respiratory changes in ventricular dimensions
 - Right and left atrial and ventricular diastolic collapse

- Abnormal respiratory variation in tricuspid and mitral flow velocities
- Dilated inferior vena cava (IVC) with lack of inspiratory collapse (IVC plethora)
- Swinging heart with large pericardial effusion

Echocardiographic Findings of Pulmonary Embolism

- A TTE can be used with serum biomarkers (troponin, B-type natriuretic peptide) to assess right ventricle (RV) strain
 - TTE should not be used as sole means of diagnosis but is helpful in guiding management
 - Patients with significant right ventricular strain are at increased risk of death and may benefit from thrombolytic therapy
- 40% of patients with pulmonary embolism have abnormalities of the RV
- Abnormal findings on TTE include:
 - RV enlargement and systolic dysfunction
 - Ventricular septal flattening and paradoxical septal motion (or intraventricular septal contour abnormalities related to RV pressure overload and interdependence of the ventricles)
 - Thrombus in transit through right heart may be visualized in 10% of patient with pulmonary embolism; in the setting of pulmonary embolism, emboli are evident in the pulmonary arteries in as many as 58% of transesophageal echocardiograms (TEEs) but are rarely seen in TTE studies
 - Tricuspid and pulmonary regurgitation may be present, particularly in the setting of right ventricular and pulmonary artery enlargement
 - Tricuspid regurgitant velocities can be used to estimate pulmonary artery pressures: a mean pulmonary artery pressure more than 40 mm Hg is unlikely in the setting of isolated acute pulmonary

embolism but can be present in the setting of chronically elevated pulmonary artery pressures

- Qualitative assessment of pulmonary arterial hypertension by a rapid pulmonary acceleration time from the Doppler flow velocity of the right ventricular outflow tract
- For many of these findings to be present, the embolism must be hemodynamically significant, obstructing more than 25% of the pulmonary vascular bed^{3,4}
- A large pulmonary embolism may be associated with normal contraction and “sparing” of the right ventricular apex despite moderate/severe RV free wall hypokinesis (McConnell’s sign)
 - This serves as a good screening tool to differentiate RV dysfunction due to pulmonary embolism from primary pulmonary hypertension³
- Thrombolytics should be considered in patients with pulmonary embolism who are hemodynamically unstable and have moderate to severe RV dysfunction
 - Serial TTEs may be used to evaluate RV function after thrombolytics

Echocardiographic Findings of Mechanical Complications After Myocardial Infarction

- Left ventricular free wall rupture usually results in sudden death
 - Rarely, subacute rupture can be manifested by pericardial pain, rub, and electrocardiogram consistent with pericarditis; occurs 1-7 days after myocardial infarction (MI); there are three types:
 - Slitlike tear early post-MI at junction of infarcted and normal myocardium
 - A subacute process with localized necrosis
 - Rupture preceded by thinning of the muscle
- Pericardial effusion

- High acoustic echoes in pericardium suggesting blood clot or tear in myocardium
- Ventricular septal rupture (clinical triad: new systolic murmur, palpable thrill, and congestive heart failure/shock)
 - 50%-60% following anterior MI (usually direct course, apical septum), 40%-50% after inferior MI (may be serpeginous course, inferior septum)
 - Defect may be seen with two-dimensional imaging; left to right ventricular shunt evident using color Doppler
 - RV overload pattern⁵
- Acute mitral regurgitation (MR)
 - May be secondary to ischemic papillary muscle, papillary muscle rupture, LV dilation, or chordal rupture (see section titled Complications Following Myocardial Infarction)
 - TTE often but does not always show regurgitant flow by color Doppler. In setting of severe acute regurgitation there may be no murmur, no turbulent regurgitant jet, and no apparent MR; two-dimensional imaging can show flail papillary muscle or leaflet
 - May need TEE to establish diagnosis in some instances

Echocardiographic Findings of Infectious Endocarditis⁶

- Endocarditis is a semiurgent indication for echocardiography
 - When a patient is hemodynamically unstable and endocarditis is strongly suspected on clinical grounds
- TTE may be inadequate in 15%-20% of patients due to obesity, chronic obstructive pulmonary disease, and chest wall deformity

- Sensitivity 50%-60%
- Features present in TTE may include vegetation, valvular regurgitation, myocardial abscess, pericardial effusion, and prosthetic valve dysfunction
- TEE raises sensitivity for detecting vegetations without loss of specificity

Echocardiographic Findings of Aortic Dissection

- The International Registry of Acute Aortic Dissection (IRAD) review showed⁷
 - Computed tomography (CT) was performed in 61%
 - Echocardiogram in 32%
 - Aortography in 4% of a cohort of patients with aortic dissection
 - 12.4% of these patients had no mediastinal widening on chest x-ray
- Noninvasive imaging techniques including multi-plane TEE, CT, and magnetic resonance imaging (MRI) have replaced angiography as diagnostic tests of choice (for details, see section titled Aortic Dissection)
- TTE is inadequate to exclude aortic dissection but can help assess for complications of dissection, including aortic insufficiency, pericardial effusion and tamponade, and new ventricular wall motion abnormalities that may result from coronary involvement in the dissection.
- In the hemodynamically unstable patient, multi-plane TEE is the most convenient study with high sensitivity
 - Intimal dissection flaps as well as true and false lumens are diagnosed with high resolution
 - MRI has excellent sensitivity as well but is not readily available
 - CT is the most commonly ordered study

References

- ③ 1. Fowler NO. Cardiac tamponade. A clinical or an echocardiographic diagnosis? *Circulation* 1993;87:1738-41.
- ③ 2. Spodick DH. Current concepts: Acute cardiac tamponade. *N Engl J Med* 2003;349:684-90.
- ③ 3. Goldhaber SZ. Echocardiography in the management of pulmonary embolism. *Ann Intern Med* 2002;136:691-700.
- ③ 4. Goldhaber SZ. Medical progress: Pulmonary embolism. *N Engl J Med* 1998; 339:93-104.
- ③ 5. Birnbaum Y, Fishbein MC, Blanche C, et al. Current concepts: Ventricular septal rupture after acute myocardial infarction. *N Engl J Med* 2002;347:1426-32.
- ③ 6. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* 2004;345:1318-30.
- ① 7. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): New insights into an old disease. *JAMA* 2000;283:897-903.

INDICATIONS FOR ELECTROPHYSIOLOGICAL (EP) TESTING

Definitions

- Requires the placement of multiple electrode catheters for pacing and recording in multiple cardiac chambers; usually, each catheter has multiple electrical poles for pacing and recording

General Indications

- Programmed electrical stimulation can reproduce induced supraventricular and ventricular arrhythmias in a controlled laboratory setting
- Perform to obtain an accurate diagnosis (i.e., type and mechanisms of arrhythmia)
- May be performed for therapeutic purposes (i.e., ablation)
- To assess the future risk of serious arrhythmic events (e.g., in symptomatic patients with syncope)

and/or palpitations, especially in patients with undocumented arrhythmias)

- Guiding and assessing pharmacological therapy

Specific Indications¹

Diagnosis and Management of Bradyarrhythmias

- Sinus node dysfunction
- Atrioventricular (AV) block; determining level of AV block
- Intraventricular conduction delay

Diagnosis and Management of Tachyarrhythmias

- Narrow complex tachycardia; wide complex tachycardia
- Congenital syndromes (i.e., long QT or Brugada's syndrome)
- Wolff-Parkinson-White syndrome
- To reproduce narrow or wide complex tachycardia for "mapping" purposes and, ultimately, ablation

Syncope of Unknown Etiology

- Especially in patients with structural heart disease that remains unexplained after appropriate evaluation
- Assess the cardiac conduction system (e.g., sinoatrial, atrioventricular nodes, and Purkinje's muscle fibers) for viability and inducible arrhythmias that may contribute to the syncopal event

Primary Prevention of Sudden Cardiac Death

- To search for electrophysiological, inducible, sustained ventricular tachycardia and ventricular fibrillation in patients with high-risk factors (e.g., coronary artery disease, depressed left ventricular systolic function, and nonsustained ventricular

tachycardia) for possible implantable cardioverter defibrillator (ICD) therapy.

Other Uses

- Determine the optimal parameters for ICDs
- Determine the mechanisms of unexplained palpitations in patients with a negative loop or event recording
- Determine the efficacy of antiarrhythmic drugs on supraventricular and ventricular arrhythmias (rare)



Patient Care Warnings

- Contraindications²
 - Unstable angina
 - Bacteremia or sepsis
 - Acute decompensated congestive heart failure not caused by an arrhythmia
 - Significant bleeding diathesis
 - Lower extremity venous thrombosis, especially if femoral vein cannulization is preferred

References

- ③ 1. Zipes DP, et al. Guidelines for clinical intracardiac electrophysiological and catheter ablation procedures: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Intracardiac Electrophysiologic and Catheter Ablation Procedures). Developed in Collaboration with the North American Society of Pacing and Electrophysiology. JACC 1995;26:555-73.
- ③ 2. Tracy CM, et al. American College of Cardiology/American Heart Association clinical competence statement on invasive electrophysiologic studies, catheter ablation, and cardioversion. JACC 2000;36:1725-36.

PACEMAKERS AND DEFIBRILLATORS

Permanent Pacemakers

REVISED NBG PACING NOMENCLATURE

Position I	Position II	Position III	Position IV	Position V
Chamber(s) Paced	Chamber(s) Sensed	Response to sensed contraction	Programma- bility and rate modu- lation	Multisite pacing
(D, A, V, O)	(D, A, V, O)	(D, I, T, O)	(O, R)	(D, A, V, O)

D = Dual = (A + V) or (T + I); A = right atrium; V = right ventricle; O = none; I = pacemaker pulse inhibited; T = pacemaker pulse triggered; R = rate modulation; P = simple programmable; M = multiprogrammable; C = communicating

Adapted from Bernstein AD, Daubert JC, Fletcher RD, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing: North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. PACE 2002;25:260-64.

Choice of Pacing Mode¹

- If evidence exists for atrioventricular (AV) nodal disease, bundle of His disease, bundle branch block (BBB), or need for pharmacological treatment with AV nodal blockers, DDD should be used to preserve AV synchrony; however, if there is no organized atrial activity (as in chronic atrial fibrillation), VVI can be used; randomized studies have not shown benefit for DDD over VVI in elderly patients with heart block; the general practice is to preserve AV synchrony but has not been shown
- If there is a concern for intermittent atrial tachyarrhythmias, DDI can be used to prevent tracking the atrial tachycardia, or turn on the mode-switching option
- Patients whose heart rate (HR) does not respond

appropriately to activity should have rate-adaptive pacing systems, although there are few data to support this function

- A magnet placed over a pacemaker generator can change any mode to asynchronous pacing (VOO/DOO)

Indications¹⁻⁴

Sinus Node Dysfunction

- Indication for >50% of all permanent pacemakers (PPMs)
- Class I: symptomatic
- Class II: HR <40 bpm (no clear association between symptoms and bradycardia)
- Recommended pacing modes: AAI, DDD, DDDR, DDIR

Acquired AV Block

- Class I
 - Symptomatic second or third degree
 - Asymptomatic third degree and HR $\leq$ 40 bpm or asystole $\geq$ 3.0 sec
 - Consequence of post-AV junction ablation
- Class II
 - Asymptomatic second-degree type 2
 - Asymptomatic third degree and HR >40 bpm
 - Asymptomatic second-degree type 1 at infra- or intra-His levels
- Recommended pacing modes: DDD, VVI, DDDR, VVIR

Bifasicular or Trifasicular Block

- Class I
 - With symptomatic intermittent third-degree AV block
 - With intermittent second-degree type 2 AV block

- Class II
 - His-ventricular interval >100 msec
 - Associated with syncope
- Recommended pacing modes: DDD, VVI, DDDR, VVIR

Neurogenic Syncope

- Class I
 - >3 sec of asystole induced by minimal carotid-sinus pressure plus recurrent syncope clearly provoked by carotid-sinus stimulation
- Class II
 - Recurrent syncope and hypersensitive cardioinhibitory response without a clear association
 - Associated with bradycardia reproduced by head-up tilting after medical therapy has failed
- Recommended pacing modes: DDD, DDI

Cardiomyopathy

- Class I: none
- Class II: symptomatic hypertrophic obstructive cardiomyopathy (HOCM)
- Recommended pacing modes: DDD, DDDR

Postmyocardial Infarction (Post-MI)

- Class I
 - Persistent type 2 AV block with bilateral BBB
 - Third-degree AV block, with the block within or below His-Purkinje system
 - Transient infranodal second- or third-degree AV block associated with a BBB
 - Persistent and symptomatic second- or third-degree AV block
- Class II
 - Persistent second- or third-degree AV block at the AV node

- Recommended pacing modes: DDD, VVI, DDDR, VVIR

Tachyarrhythmias

- Class I
 - History of sustained pause-dependent ventricular tachycardia (VT) shown to be responsive to pacing
- Class II
 - Symptomatic recurrent supraventricular tachycardia for which catheter ablation or pharmacological treatment is ineffective or intolerable
 - High-risk patients with congenital long QT syndrome

Pacemaker Complications^{5,6}

Failure to Sense

- Causes
 - Inadequate signal, low pacemaker sensitivity, lead malposition, lead failure
- Clinical presentation
 - Inappropriate pacing
- Management
 - Increase sensitivity of pacemaker empirically, reposition leads, replace leads

Loss of Capture

- Causes
 - Battery depletion, lead malposition, inflammation of electrode tip, lead failure, increase in capture threshold, low pacemaker output
- Clinical presentation
 - Bradycardia
- Management
 - Change battery, reposition leads, replace leads, change settings

Pacemaker Syndrome

- Caused by the loss of AV synchrony, typically seen with VVI (atrium contracts irrespective of ventricular function)
- Low cardiac output and elevated atrial pressures in a patient with a normally functioning pacemaker in the absence of other causes
- Clinical presentation
 - Presyncope, syncope, congestive heart failure (CHF), throbbing sensation in neck and/or chest
- Management
 - Switch or upgrade to DDD

Pacemaker-Mediated Tachycardia (PMT)

- Endless loop tachycardia
 - A ventricular premature beat causes retrograde conduction from ventricle to atrium; in a DDD PPM, the retrograde P wave is sensed by the atrial lead and triggers ventricular contraction and initiation of the tachycardia
- Tracking of native atrial tachyarrhythmia
 - In a DDD pacer, atrial activity is sensed during atrial tachyarrhythmias and triggers a rapid ventricular response
 - Automatic mode switch algorithm should limit this form of tachycardia
- Management
 - Terminate with a magnet placed over pacemaker generator
 - Will ultimately require a change in pacemaker settings

Crosstalk

- Occurs in DDD pacers, caused by the ventricular lead sensing an atrial contraction; the pacing system erroneously assumes there was an intrinsic ventricu-

lar contraction and, as a result, inhibits the pacemaker pulse to the ventricle

- Clinical presentation
 - With an intact AV nodal system, this phenomenon is usually asymptomatic; however, with AV nodal disease, in particular third degree AV block, this can result in diminished ventricular activity resulting in presyncope, syncope, CHF, or asystole
- Management
 - Decrease sensitivity of the ventricular sensor or increase refractory time of ventricular sensor during atrial contraction

Pacemaker Infections

- Clinical presentation
 - Varied spectrum: subtle inflammation over implanted device, erosion of device through skin, constitutional symptoms, sepsis, or endocarditis
- Management
 - Antibiotic therapy, removal of entire pacing system, replacement of pacing system

Implantable Cardioverter Defibrillators (ICDs)

Indications^{2,6,7}

Class I

- Cardiac arrest due to VT or ventricular fibrillation (VF) not due to a transient or reversible cause
- Episode of spontaneous sustained VT and structural heart disease
- Episode of spontaneous sustained VT and no other treatment options

- Syncope of unknown etiology and sustained VT or VF induced at electrophysiology (EPS)
- Nonsustained VT in the presence of coronary artery disease, prior MI, and LV dysfunction with sustained VT or VF induced at EPS

Class II

- New York Heart Association (NYHA) II/III, left ventricular ejection fraction (LVEF) $\leq 30\%$, ischemic dilated cardiomyopathy (DCM), prior MI, or nonischemic DCM >9 mo (exclusions: NYHA IV; MI within 3 months; coronary artery bypass grafting/percutaneous transluminal coronary angioplasty within 3 months)
- Sudden cardiac death (SCD) presumed to be due to VF when EPS precluded by other medical conditions
- Sustained VT or with severe symptoms (e.g., syncope) in patients awaiting cardiac transplantation
- Familial or inherited conditions with high risk of unexplained SCD in association with RBBB pattern and ST elevation (Brugada's syndrome)
- Familial or inherited conditions with a high risk for life threatening VT (congenital long QT syndrome)
- Unexplained syncope in patient with structural heart disease when thorough investigation has failed to find cause

Evidence^{7,8}

Primary Prevention Trials

- MADIT⁸ and MUSTT⁹: nonsustained VT, ischemic disease/prior MI, depressed LVEF, and inducible sustained VT
- MADIT II¹⁰ ischemic disease/prior MI and LVEF $<30\%$
- DEFINITE¹¹ nonischemic dilated cardiomyopathy

treated with angiotensin-converting enzymes and beta blockers, LVEF = 35%, and ventricular premature beats or nonsustained VT; ICD reduces risk of death from SCD

- DINAMIT¹² prophylactic ICD does not reduce overall mortality in high-risk patients who have recently had an MI
- SCD-HeFT¹³ NYHA II or III CHF regardless of etiology and LVEF $\leq 35\%$; single lead shock therapy is superior to amiodarone in reducing overall mortality

Secondary Prevention Trials

- CASH¹⁴ cardiac arrest due to VT/VF
- CIDS¹⁵ and AVID¹⁶ cardiac arrest due to VT/VF or hemodynamically important VT

Complications^{7,8}

- Failure to sense or failure to defibrillate
 - Causes: battery depletion, lead dislodgement, lead insulation defect, generator failure
 - Management: replace battery, reposition leads, replace leads, replace generator
- Electrical storm
 - ≥ 3 consecutive appropriate shocks for repeated episodes of VT or VF within 24 hours
 - Causes: myocardial ischemia, electrolyte abnormalities, heart failure resulting in increased sympathetic tone; in 80% of cases, no cause can be determined
 - Management: treat underlying abnormality, utilize beta blockers and intravenous amiodarone
- Inappropriate shocks
 - Causes: supraventricular tachycardias, nonsustained VT, electrical noise, ICD malfunctioning, inappropriate sensing
 - Management: antitachycardia pacing, antiarrhythmic drugs, catheter-based ablation

- Proarrhythmia: incidence of supraventricular tachycardias increases after a shock; if these result in a rapid ventricular response, AICD may continue to fire inappropriate shocks and infections
- See the previous section on pacemaker infections



Patient Care Warnings

- Magnetic resonance imaging (MRI) should not be performed on patients with ICDs or pacemakers; however, if an MRI is absolutely necessary, consult with an electrophysiologist about the possibility of reprogramming the cardiac device to facilitate the procedure

References

- ③ 1. Kusumoto FM, Goldschlager N. Cardiac pacing. *N Engl J Med* 1996;334:89-98.
- ③ 2. Gregoratos G, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices. *Circulation* 2002;106:2145-61.
- ③ 3. Kusumoto FM, Goldschlager N. Device therapy for cardiac arrhythmias. *JAMA* 2002;287:1848-52.
- ③ 4. Trohman RG, Kim MH, and Pinski SL. Cardiac pacing: The state of the art. *Lancet* 2004;364:1701-19.
- ③ 5. Ausubel K, Furman S. The pacemaker syndrome. *Ann Intern Med* 1985;103:420-29.
- ③ 6. Hayes DL, Zipes DP. Cardiac pacemakers and cardioverter-defibrillators. In Braunwald: *Heart Disease: A Textbook of Cardiovascular Medicine*, 6th ed. Philadelphia, WB Saunders, 2001:775-814.
- ③ 7. DiMarco JP. Implantable cardioverter-defibrillators. *N Engl J Med* 2003;349:1836-47.
- ① 8. Moss AJ, Hall WJ, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933-40.
- ① 9. Buxton AE, Lee KL, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882-90.
- ① 10. Moss AJ, Zareba W, et al. Prophylactic implantation of a

defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83.

11. Kadish A, Dyer A, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350:2151-58.
12. Hohnloser SH, Kuck KH, Dorian P, et al. DINAMIT Investigators: Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-88.
13. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:2146.
14. Kuck KH, Cappato R, Siebels J, et al. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: The Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;102:748-54.
15. Connolly SJ, Gent M, et al. A randomized trial of the implantable cardioverter-defibrillator against amiodarone. *Circulation* 2000;101:1297-1302.
16. AVID Investigators. A comparison of anti-arrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-83.

PULMONOLOGY

CHRONIC OBSTRUCTIVE LUNG DISEASE

Definition, Etiology, and Epidemiology

- Chronic respiratory disease characterized by airflow limitation ($FEV_1/FVC < 0.7$) not fully reversible; usually progressive and associated with abnormal inflammatory response to noxious gases or particles
- Chronic bronchitis: clinically defined as chronic cough with sputum lasting at least 3 mo for at least 2 y
- Emphysema: pathological definition referring to loss of alveolar-capillary units
- Bronchiectasis: permanently destroyed/dilated bronchi
- Etiology
 - Inhalants: cigarette smoke (cause in 85%-90% of cases) recruits macrophages and neutrophils into airways → release of proteases (elastase) and oxide radicals → tissue damage, mucus hypersecretion → cough, sputum, increased expiratory flow resistance, reduced exercise capacity, air-trapping, decreased diffusion capacity (DLCO)
 - α_1 -antitrypsin deficiency
 - Chronic infections: airway colonization by *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus influenzae*
 - Occupational exposures: coal dust, cadmium, etc.
- Affects 16.4 million persons in United States, 53 million worldwide
- Fourth leading cause of death: accounted for 2.7

million deaths in 2000; also the only leading causing with a rising mortality rate

- Over 500,000 hospitalizations per year, 11% in-hospital mortality rate¹

Pearls of the History and Physical Examination

- Chronic tobacco use
- Chronic shortness of breath, dyspnea, hypoxemia, orthopnea (relieved within minutes by coughing), and cough
- Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages of chronic obstructive pulmonary disease (2003 update)²

Stage 0: At risk	FEV ₁ /FVC <0.7, normal spirometry
Stage 1: Mild	FEV ₁ /FVC <0.7, FEV ₁ >80%
Stage 2: Moderate	FEV ₁ /FVC <0.7, FEV ₁ >50% and <80%
Stage 3: Severe	FEV ₁ /FVC <0.7, FEV ₁ >30% and <50%
Stage 4: Very severe	FEV ₁ /FVC <0.7, FEV ₁ <30%
- Acute exacerbation (symptoms and etiology)
 - Worsening dyspnea, cough, sputum production, respiratory failure
 - Primary causes: tracheobronchial infection (*H. influenzae*, *S. pneumoniae*, *M. catarrhalis*), air pollution
 - Secondary causes: pneumonia, pulmonary embolism, pneumothorax, chest trauma, drugs (sedatives, narcotics, beta blockers), heart failure, cardiac arrhythmias, myocardial infarction
- Acute exacerbation (physical examination findings)
 - Tachypnea, hypoxemia, use of accessory muscle of respiration, paradoxical abdominal motion
 - Distant heart sounds, tachycardia, pulsus paradoxus
 - Right heart failure, peripheral edema
 - Wheezing, rhonchi, hyperinflated lung fields

- Central cyanosis and altered mental status merit urgent test of arterial blood gas (ABG) and consideration of artificial ventilation

Diagnostic Studies and Laboratory Values

- Chest x-ray
 - Hyperinflated lung fields, bullae
 - Evaluate for pneumothorax, pneumonia, chest wall trauma, rib fractures
- Laboratory values
 - ABG: hypoxia, hypercapnia; the usual finding is ventilatory failure with an increased A-a O₂ gradient
 - Complete blood count: leukocytosis (infection), polycythemia
 - Chem-10: electrolyte disturbance, acid-base status
- Electrocardiogram may reveal right axis deviation, poor R-wave progression, arrhythmias
- Sputum culture should be sent if purulent sputum present
- Consider ruling out other causes such as myocardial ischemia/infarction, thromboembolism, etc.

Guide to Acute Management

- Assess severity of symptoms, ABG abnormalities, chest x-ray

Treatment	Dose/Comments	Notes
Oxygen	Titrate for O ₂ sat 90%-93% (PaO ₂ 60-65 mm Hg)	Decreases mortality ³
Bronchodilators β ₂ -agonists Anticholinergics	Albuterol MDI or nebulized q 2-6 hr <i>also</i> fenoterol, metaproterenol, terbutaline ipratropium MDI or nebulized q 2-6 hr	First line by GOLD recommendations ² Increases FEV ₁ , especially if reactive airways disease

(Continued on following page)

Treatment	Dose/Comments	Notes
Glucocorticoids	Ideal dose uncertain: Prednisone 30-40 mg po every day $\times$ 10-14 d High dose: Methylprednisolone 125 mg IV q 6hr $\times$ 72 hr; then prednisone 60 mg po every day $\times$ 4 d and taper by 20 mg every 4 d	First line by GOLD recommendations ² Less tachycardia, increases FEV ₁ , preferred Rx in setting of acute coronary syndrome and cardiac arrhythmias Accepted dose for maximal effect with minimal complications (e.g., diabetes, hypertension, myopathy, psychosis) ² Reserve for moderate to severe exacerbations and low risk for side effects Improves FEV ₁ after 12-24 hr
Antibiotics	For exacerbations characterized by increased sputum and purulence; limited data regarding appropriate regimen. Amoxicillin, TMP-SMX, doxycycline historically preferred ⁵ ; also consider macrolides, cephalosporins, quinolones	<i>S. pneumonia</i> , <i>H. influenza</i> , <i>M. catarrhalis</i> most common pathogens ⁵
Methxanthines	Theophylline 150-450 mg po bid loading dose or aminophylline 0.9 mg/kg/hr IV loading dose followed by maintenance dose (check levels)	For severe exacerbations not improving with above therapies Monitor levels and side effects (headache, insomnia, arrhythmias, convulsions); metabolized by P450 enzymes (thus many drug interactions)
Noninvasive positive pressure ventilation (NIPPV) ^{2,6}	Moderate to severe dyspnea and acidosis (pH <7.35), hypercapnia (Paco ₂ >60 mm Hg), tachypnea (RR >25)	Avoid in respiratory failure, cardiovascular instability, somnolence, high aspiration risk, recent facial or gastric trauma or surgery, extreme obesity

Treatment	Dose/Comments	Notes
Invasive ventilation ²	Severe dyspnea and acidosis ($\text{pH} < 7.25$, $\text{RR} > 35$); severe hypoxemia ($\text{PaO}_2 < 40$ mm Hg or $\text{PaO}_2/\text{FiO}_2 < 200$); hypercapnea ($\text{PaCO}_2 > 60$ mm Hg), respiratory arrest, or when NIPPV is not an option or fails	Initial setting: 15-20 cm H_2O inspiratory pressure, 5 cm PEEP, titrate to tidal volume of 5-7 mL/kg Requires close observation with serial ABGs in first several hours Achieving synchrony between patient and ventilator is essential 17%-30% mortality
Other measures	IV hydration, nutrition, deep venous thrombosis prophylaxis	



Patient Care Warnings

- Always attempt to determine patient's wishes prior to proceeding with invasive mechanical ventilation when possible
- When initiating supplemental oxygen therapy in patients with COPD, make sure to monitor for CO_2 retention; consider checking an ABG 30 minutes after beginning oxygen
- Oxygen should be titrated for saturations of 90%; many of these patients rely on their hypoxic drive for ventilation; aggressive supplementation may provoke ventilatory failure

References

- ③ 1. Stoller JK. Acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002;346:988-94.
- ③ 2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. NHLBI/WHO Workshop Report. Bethesda, National Heart, Lung, and Blood Institute, April 2001; Update of the Management Sections, GOLD website (www.goldcopd.com). Updated: July 1, 2003.
- ③ 3. Calverley PM, Walker P. Chronic obstructive pulmonary disease. *Lancet* 2003;362:1053-61.
- ① 4. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999;340:1941-47.
- ① 5. Anthonisen NR, Manfreda J, Warren CP, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196-204.
- ① 6. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: A multicentre randomised controlled trial. *Lancet* 2000;355:1931-35.

THE OTHER OBSTRUCTIVE LUNG DISEASES

Asthma

Definition, Etiology, and Epidemiology¹

- Chronic inflammatory disorder of the airways, characterized by recurrent episodes of increased airflow limitation and airway hyper-responsiveness to various stimuli; stimuli may include allergens, environmental irritants, viral infections, cold air, and exercise
- Pathological findings include infiltration of mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells
- Categories²
 - Childhood asthma
 - Asthma persisting from childhood to adulthood

- Adult-onset asthma: aspirin-induced asthma, asthma related to chronic persistent respiratory infection, occupational asthma; immunological and nonimmunological
- Three clinical patterns of severe asthma³
 - Near-fatal asthma: includes severe exacerbations characterized by recurrent emergency room visits and hospitalizations during the preceding year
 - Asthma with fixed airflow obstruction: an end effect of chronic inflammation and remodeling; occurs in 35%-50% adults
 - Steroid-resistant asthma
- Almost 500,000 hospitalizations annually and more than 5000 deaths per year attributed to asthma
 - Children and blacks at highest risk; most deaths occur in blacks age 15-24 years

CLASSIFICATION OF ASTHMA AT BASELINE IN ADULTS AND CHILDREN*

Classification	Symptoms	Nighttime symptoms	Predicted Pulmonary Function Tests
Mild intermittent	Twice/week or less Brief exacerbations Normal peak expiratory flow (PEF) between exacerbations	Two nights/month or less	PEF or FEV ₁ >80%
Mild persistent	Twice/week but < once/day Exacerbations may affect activity	>Two nights/month	PEF or FEV ₁ >80%
Moderately persistent	Daily Exacerbations may last days Affects activity	>One night/week	PEF or FEV ₁ 60%-80%
Severely persistent	Continuous Limited physical activity Frequent exacerbations	Frequent	PEF or FEV ₁ <60%

*Modified from reference 1

Pearls of the History and Physical Examination

- Ask how many exacerbations per year, how many days missed from work/school, history of hospitalizations or intubations
- Episodic airflow obstruction: difficulty breathing, chest tightness, cough (especially nocturnal), wheezing, exercise-induced symptoms
- Tachypnea, respiratory distress, use of accessory muscles, wheezing, prolonged expiration phase, paradoxical thoracoabdominal movement, nasal flaring
- Tachycardia
- Can also observe increased nasal secretions and polyps, atopic dermatitis, gastroesophageal reflux disease

CLASSIFYING SEVERITY OF EXACERBATIONS*

Symptom or finding	Mild	Moderate	Severe	Impending respiratory arrest
Breathlessness	While walking	While talking	While at rest	Severe
Alertness	May be agitated	Agitated	Agitated	Drowsy or confused
Wheeze	Moderate end-expiratory	Loud, through expiration	Loud, inhalation and exhalation	Absent
Pulse	<100	100-120	>120	Bradycardia
PEF (% personal best)	>80%	50%-80%	<50%	<50%
pO ₂ mm Hg (SaO ₂ %)	Normal (>95%)	>60 (91%-95%)	<60 (<91%)	<60 (<91%)
pCO ₂ mm Hg	<42	<42	>42	>42

*Modified from reference 1

Diagnostic Studies and Laboratory Values

- Acute exacerbation
 - O₂ saturation
 - Arterial blood gas

- PEF rate (most useful if patient knows his/her own baseline)
- Chest x-ray: rule-out pneumonia, pneumothorax, atelectasis, congestive heart failure
- Electrocardiogram (ECG) may show right ventricular strain pattern
- Complete blood count (CBC), serum electrolytes, serum theophylline level
- Pulmonary function testing is rarely used in acute setting

Guide to Acute Management

THERAPY IN ASTHMA EXACERBATIONS*		
Treatment	Dose/Comments	Notes
Oxygen	Maintain saturations >90% (>95% in pregnant women and CHF patients)	Monitor continuously
Inhaled β_2 -agonists (short acting) First-line agents	Albuterol Nebulizer 2.5-5 mg every 20 min, then 2.5-10 mg every 1-4 hr or 10-15 mg/hr continuous Bitolterol Nebulizer (2 mg/mL) as above Pirbuterol	Metered dose inhaler (MDI) (90 μ g/puff) can be used if patient able to comply 4-8 puffs q 20 min up to 4 hr, then 1-4 hr as needed MDI (370 μ g/mL) is available; do not mix with other medications (such as anticholinergics) MDI (200 μ g/puff) is available
Systemic β_2 -agonists	Epinephrine 1:1000 (1 mg/mL) 0.3-0.5 mg every 20 min $\times$ 3 doses, then every 2-4 hr Terbutaline (1 mg/mL) 0.25 mg every 20 min $\times$ 3 doses	Not first-line therapy No proven efficacy over inhaled β_2 -agonists

(Continued on following page)

THERAPY IN ASTHMA EXACERBATIONS* (Continued)

Treatment	Dose/Comments	Notes
Anticholinergics	Ipratropium bromide Nebulizer 0.5 mg every 30 min $\times$ 3 doses, then every 2-4 hr as needed	Not first-line; mix with albuterol; MDI is available but dose is low and has not been studied
Steroids	Prednisone Ambulatory "pulse": 40-60 mg once or divided twice daily for 3-10 days Moderate to severe exacerbations: methylprednisolone 120-180 mg/d in 3-4 doses for 48 hr, then 60-80 mg/d until PEF >70%	Give as soon as possible; equivalent doses of methylprednisolone or prednisolone can be used; no proven benefit of IV vs. oral steroids Steroid therapy decreases time to discharge; taper dose up to 2-3 weeks to prevent recurrence; no proven benefit of inhaled steroids in acute setting
Less proven therapies usually reserved for severe exacerbations	Heliox: give with bronchodilators (80% He/20% O ₂) MgSO ₄ (2 mg IV over 20 min) Antileukotriene agents Anti-IgE immunotherapy	Lower density than air; therefore, decreases airway resistance and improves drug deposition in smaller airways Bronchodilatory effect; nebulized MgSO ₄ mixed with bronchodilators has been used in some centers Inadequate proof of efficacy in acute setting Used in severe allergic asthma
Mechanical ventilation (MV):NIPPV Intubation	Use only in cooperative, alert patients Perform sooner rather than later	MV in asthma is difficult, given the high airway resistance and physiological effects of dynamic hyperinflation, and should be managed in an intensive care unit by highly qualified specialists; "permissive hypercapnia" and "inverse ratio ventilation" are common strategies

*Modified from references 1 and 4

- Methylxanthines are not generally recommended¹
- Use antibiotics only if bacterial infection is suspected



Patient Care Warnings

- Severe exacerbations that require mechanical ventilation carry up to 30% in-hospital and post-hospitalization mortality
- Avoid aspirin, beta blockers, sulfates, or other allergens in those who are sensitive
- Post-discharge therapy for moderate to severe asthma includes long-acting beta agonists, steroids (oral taper and inhaled forms), peak expiratory flow monitoring, and close follow-up; consider also possibly adding a leukotriene-modifying agent

Bronchiectasis

Definition, Etiology, and Epidemiology⁵

- Permanent irreversible dilation of bronchi and bronchioles due to chronic cycle of transmural infection, inflammation, and cytokine release
 - Focal disease: airway occlusion by foreign body, tumor, extrinsic compression of lymph node, or postlobectomy changes
 - Diffuse disease: associated with chronic systemic diseases
 - Morphology definitions:
 - Tubular (or cylindrical)

- Varicose
- Cystic
- Causes/disease associations⁶
 - Recurrent infections (*Pseudomonas*, mycobacteria, aspergillus/allergic bronchopulmonary aspergillosis [ABPA], and others)
 - Cystic fibrosis
 - Ciliary dyskinesia
 - Immunoglobulin deficiency
 - Connective tissue diseases; rheumatoid arthritis
 - Inflammatory bowel disease
- Prevalence unknown; more common in third world countries and areas with poor access to health care and high rates of pediatric respiratory infections

Pearls of the History and Physical Examination

- Symptoms
 - Cough, dyspnea, wheezing
 - Increased sputum production
 - Hemoptysis
 - Pleuritic chest pain
 - Fever
 - Crackles, wheezing, rhonchi
 - Clubbing

Diagnostic Studies and Laboratory Values

- Chest x-ray: may observe dilated, thickened airways with ringlike shadows or “tram lines”
- High-resolution computed tomography (CT) scan: may see dilated airways, varicose airways, cysts at ends of bronchi, mucus plugging; usually affects lower lungs
- Pulmonary function tests: can be characterized by

decreased FEV₁, normal to slightly reduced forced vital capacity (could indicate mucus-blocked airway), bronchodilator response in up to 40% of patients

- CBC
- Blood and sputum cultures
- Consider quantitative immunoglobulin levels, rheumatoid factor, aspergillus precipitins (allergic bronchopulmonary aspergillosis [ABPA]), cystic fibrosis gene (CFTR) testing

Guide to Acute Management⁵

- Antimicrobials
 - Should empirically cover for common potential pathogens such as *Haemophilus influenzae* (55%), *Pseudomonas* species (26%), *Streptococcus pneumoniae* (12%)⁷
 - Quinolones (levofloxacin or ciprofloxacin) and macrolides (clarithromycin, azithromycin, erythromycin) are good first choices
 - Inhaled aerosolized antimicrobials may have efficacy
 - Consider itraconazole for ABPA
- Chest physiotherapy and related mucus clearance strategies
- Steroids: inhaled fluticasone 500 µg bid decreases inflammatory indices but no improvement in pulmonary function⁸; no proven efficacy of oral steroids
- Respiratory failure: noninvasive ventilation strategies are preferred over intubation and lead to better outcomes⁹
- Surgical resection for localized disease that is nonresponsive to therapy, massive hemoptysis, and lung abscess



Patient Care Warnings

- Diagnosis depends on morphological appearance on CT scan
- Usually affects lower lobes but may affect upper lobes when associated with cystic fibrosis and/or ABPA
- Chronic suppressive antibiotic therapy can help prevent exacerbations in outpatient settings
- Poor prognostic factors: age >65 years, long-term oxygen therapy⁹

References

- ③ 1. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma: Expert panel report 2. Bethesda, MD,: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 1997; <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>
- ③ 2. Bel EH. Clinical phenotypes of asthma. *Curr Opin Pulm Med* 2004;10:44-50.
- ① 3. Silverman RA, et al. IV magnesium sulfate in the treatment of acute severe asthma: A multicenter randomized controlled trial. *Chest* 2002;122:489-97.
- ③ 4. McFadden ER Jr. Acute severe asthma. *Am J Respir Crit Care Med* 2003;168:740-59.
- ③ 5. Barker A. Bronchiectasis. *N Engl J Med* 2002;346:1383-93.
- ③ 6. Cohen M, Sahn SA. Bronchiectasis in systemic diseases. *Chest* 1999;116:1063-74.
- ② 7. Angrill J, et al. Bacterial colonization in patients with bronchiectasis: Microbiological pattern and risk factors. *Thorax* 2002;57:15-19.
- ① 8. Tsang KWT, et al. Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis. *Am J Respir Crit Care Med* 1998;158:723-27.
- ② 9. Dupont M, et al. Survival of patients with bronchiectasis after the first ICU stay for respiratory failure. *Chest* 2004;125:1815-20.

VENOUS THROMBOEMBOLISM

Definition, Etiology, and Epidemiology

- Venous thromboembolic disease manifests as either deep vein thrombosis (DVT) or pulmonary embolism (PE)
- DVT: clot formation in the deep venous system
- PE: migration of a DVT to the pulmonary vascular system
- Massive PE: PE associated with a systolic blood pressure (SBP) <90 mm Hg or a drop in SBP by >40 mm Hg for >15 minutes that cannot otherwise be explained; usually the result of a large PE involving proximal or multiple vascular segments

Etiology and Pathophysiology

- Initiation and propagation of the coagulation cascade at a site of endothelial injury is enhanced during static or inflammatory states
- Most clinically significant PEs originate from deep venous thrombosis (DVT) in the iliofemoral venous system (proximal DVT), are multiple, and usually involve the lower lobes of the lung^{1,2}
- Ventilation/perfusion (V/Q) mismatch: secondary to vascular obstruction and local inflammation
- Pulmonary infarction: occurs in less than 10% of PE¹
- Pulmonary hypertension and right ventricular (RV) dysfunction can occur with acute and/or recurrent PE and are poor prognostic markers
- Hemodynamic collapse, shock, and death may result from RV failure

Epidemiology

- $>500,000$ patients are diagnosed with venous thromboembolism (VTE) every year in the United States

- Death within the first hour is usually the result of a massive PE
- Death within 3–6 months is usually the result of recurrent VTE with inadequate therapy³
- Mortality rates for PE^{4,5}
 - Overall: 7%-17%
 - Untreated: up to 30%
 - Treated: less than 10%
 - Massive PE: up to 30%
- Poor prognostic findings on presentation: age >70 years, tachypnea, hypotension, RV dysfunction, underlying malignancy, presence of congestive heart failure (CHF), underlying chronic obstructive pulmonary disease (COPD), syncope^{5,6}
- Risk factors for VTE:

SUMMARY OF PREDISPOSING FACTORS FOR VTE DISEASE*

Most common	Idiopathic (up to 50%) Venous manipulation Immobilization Surgery within 3 mo Malignancy History of VTE	Most patients diagnosed with idiopathic VTE have some underlying predisposing risk factor (up to 12%-17% of patients diagnosed with VTE are diagnosed with cancer within 1 y)
Highest risk	Orthopedic surgery Malignancy Thrombophilic state	Thrombophilic states include deficiencies or insufficiencies of factor V, prothrombin, protein C, S, antithrombin, etc.
Other	Age >75 years, obesity, CHF, cerebrovascular accident, pregnancy, smoking, hormone replacement therapy, inflammatory bowel disease	Most patients with DVT/PE have more than one underlying predisposing condition

*Adapted from references 7, 8, and 9

Pearls of the History and Physical Examination

- Signs and symptoms suggesting the presence of PE or DVT do not predict the presence or absence of the other⁷
 - More than 70% of patients with PE have no signs or symptoms of DVT
 - Up to 50% of patients with DVT have asymptomatic PE
- 25%-30% of patients with PE have no symptoms

SUMMARY OF COMMON SYMPTOMS AND PHYSICAL EXAMINATION FINDINGS IN PATIENTS WITH DVT AND PE*

	PE	DVT
Symptoms	Dyspnea (up to 75%) Pleurisy Cough No symptoms Nonmassive hemoptysis (up to 15%) Syncope	Leg swelling Leg pain Leg discoloration
Signs/physical findings	Tachypnea (up to 70%) Pulmonary rales (up to 50%) Tachycardia (up to 30%) S ₄ Accentuated P ₂ Fever Circulatory shock	Asymmetric calf swelling Asymmetric pitting edema Palpable cord Homan's sign (13%-48% sensitivity) Fever ($\leq 38.5^{\circ}\text{C}$)
Confounding conditions	CHF, pneumonia, myocardial infarction, pneumothorax, asthma, COPD, lung cancer, anxiety	Trauma, venous stasis, cellulitis, Baker's cyst, lymphedema

*Adapted from references 7, 10, and 11

Diagnostic Studies and Laboratory Values

- VTE may cause multiple, nonspecific laboratory abnormalities, none of which can be used for diagnosis

SUMMARY OF LABORATORY ABNORMALITIES OCCURRING IN DVT AND/OR PE

Laboratory Test	Abnormality	Comments
Arterial blood gas	Hypoxemia ($\text{PaO}_2 < 80$ mm Hg) Respiratory alkalosis Increased A-a gradient (> 20 mm Hg) Can be normal (up to 20%) in those without underlying cardiopulmonary disease	Reflects V/Q mismatch, increased dead space ventilation, and tachypnea with PE
D-dimer*	Elevated	Reflects increased endogenous fibrinolysis High negative predictive value* Poor positive predictive value (elevated in multiple other settings, including cancer, surgery, CHF, old age, etc.)
Troponin	Elevated in up to 50% with moderate/large PE	Reflects acute RV failure in acute PE and signifies an adverse prognosis
Other	Elevated erythrocyte sedimentation rate, complete blood count, lactate dehydrogenase	Look for laboratory abnormalities that may indicate an underlying predisposing state

*The ELISA D-dimer assay has been shown to have high enough NPV to merit use as an adjunct in excluding VTE in selected situations (adapted from references 7, 12, and 13)

- Electrocardiogram (ECG): nonspecific abnormalities are common (up to 70%) with PE but do not reliably predict its presence or severity^{7,14}
 - Most common finding is sinus tachycardia (50%)
 - Nonspecific ST-segment changes
 - RV “strain pattern” (acute RV failure) observed in up to 30% of PE
 - Right axis deviation, right bundle branch block, $R > S$ in V_1
 - $S > R$ in I, pathological Q in III, T-wave inversions in III ($S_1Q_3T_3$)
 - T-wave inversions in V_1 - V_3
 - ECG can also be normal
- Chest x-ray: most common abnormalities include atelectasis, effusion, cardiomegaly^{7,15}
 - Hampton’s hump (peripheral wedge-shaped infiltrate) and Westermark’s sign (focal oligemia distal to embolus) are rare¹⁴
- Lower extremity duplex ultrasound: useful in diagnosing DVT, but a negative study alone does not rule out PE^{14,16}
- Ventilation-perfusion (V/Q) scan: modest sensitivity and specificity for detecting PE^{7,14}
 - Normal V/Q result rules out PE regardless of pretest probability
 - High-probability V/Q scan with a high pretest clinical probability confirms PE
- Computed tomography (CT) angiography: very specific (70%-100%) and variably sensitive (50%-90%) for detecting clinically significant PE^{17,18}
 - Operator-dependent
 - Can miss smaller, more peripheral emboli
 - Negative study alone does not exclude PE
 - Has benefit in that one can evaluate for the presence of other pulmonary pathology
- Echocardiography: RV abnormalities common, but not specific to diagnose PE

- Pulmonary angiography: the “gold standard”; rare false-positives or false-negatives¹⁴
 - Invasive; significant morbidity

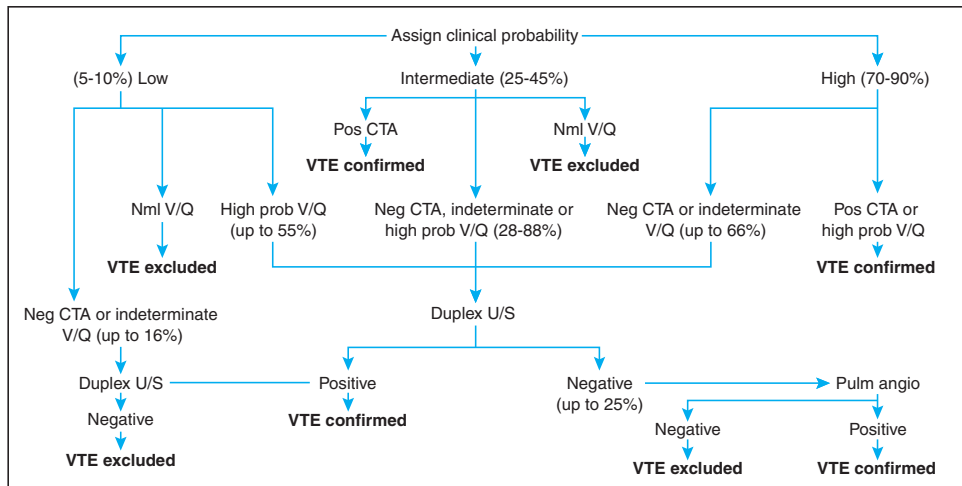
Approach to the Diagnostic Evaluation of VTE

- First calculate a pretest clinical probability
- Clinical probability of DVT
 - Of patients suspected of having a DVT, only up to 35% actually do¹⁶
 - Assigning pretest probability:
 - High: presence of certain clinical characteristics of DVT without a likely alternative diagnosis in a patient with underlying risk factors
- Clinical probability of PE
 - Of patients classified as “high” clinical probability, approximately 80% have PE
 - Of patients classified as “low” clinical probability, approximately 10% have PE
 - Assigning pretest probability:

WELLS' SCORE MODEL FOR PREDICTING PRETEST CLINICAL PROBABILITY FOR PE

Risk Factor	Probability Score
Clinical signs or symptoms of DVT	3
Alternative diagnosis less likely than PE	3
Tachycardia	1.5
Immobilization or surgery within 4 weeks	1.5
Previous DVT or PE	1.5
Active cancer within 6 months	1.0
Hemoptysis	1.0

Pretest Clinical Probability Score: Low = <2.0 , Intermediate = $2.0\text{--}6.0$, High = >6.0
(adapted from references 19 and 20)



Suggested evidence-based algorithm for the diagnostic approach to in-patient VTE. Initial imaging modality is a V/Q scan or CT angiogram. Percentages in parentheses denote possibility of PE at a given stage of diagnostic evaluation. A negative CT angiogram likely confers a higher NPV than an indeterminate V/Q. The decision tree should be individualized based on patient comorbidities and underlying illness. *D-dimer analysis not included in the algorithm; evidence does not conclusively support its standard diagnostic use for VTE in the inpatient setting. **In the setting of a low or intermediate clinical probability and nondiagnostic initial CTA or V/Q, serial duplex ultrasonography may be used to help diagnose or exclude VTE instead of pulmonary angiography if the patient is clinically stable. Pos = positive; Neg = negative; High Prob = high probability; Nml = normal; CTA = CT angiogram (helical CT); V/Q = ventilation/perfusion scan; Pulm Angio = pulmonary angiogram; Duplex U/S = lower extremity duplex ultrasound; Indeterminate V/Q refers to a V/Q scan that is either intermediate or low probability for PE (adapted from references 1, 7, and 18)

Guide to Acute Management

- Early and sufficient anticoagulation reduces the risk of recurrent VTE and death
- Intravenous unfractionated heparin (UFH) or low molecular weight heparin (LMWH) combined with warfarin is the mainstay of acute therapy^{21,22}
- IV UFH
 - 80 U/kg bolus, then 18 U/kg/hr (weight-based nomogram)
 - Continue until at least 2 days after appropriate warfarin anticoagulation
- LMWH
 - Enoxaparin 1 mg/kg q 12 hr
 - At least as medically effective and perhaps more cost-effective than IV UFH in treating nonmassive PE, without increased bleeding^{23,24}
- Warfarin
 - Initiate with heparin at 5-10 mg daily, target therapeutic international normalized ratio (INR) of 2-3²⁵
- Thrombolytic therapy
 - Only indication for tissue plasminogen activator (tPA) is PE-induced hemodynamic compromise^{22,26}
 - Benefits: more rapid thrombus resolution, lower residual pulmonary vascular resistance, rapid improvement of RV dysfunction compared with heparin^{26,27}
 - Disadvantages: bleeding (3× increased risk of serious hemorrhage)
 - No clear evidence to support thrombolytics in RV dysfunction with stable hemodynamics
 - Consider for severely compromised oxygenation with poor cardiopulmonary reserve and high chance of VTE recurrence²⁸⁻³¹
- Inferior vena cava filter³²⁻³⁴
 - No morbidity or mortality benefit over standard anticoagulation

- Complications include IV obstruction (5%-18%), venous thrombosis (up to 40%), and increased risk of lower extremity DVT (21%) at 2 years compared with standard therapy
- Use should be individualized in patients with contraindication to anticoagulation and poor cardiopulmonary reserve

SUMMARY OF ACUTE AND SHORT-TERM MANAGEMENT OF VTE

Treatment	Indications	Primary Mechanism	Comments
IV UFH 80 U/kg bolus, 18 U/kg/hr	Acute DVT/PE	Potentiates antithrombin (AT) activity	Overlap with coumadin until INR therapeutic for 2 days; caution with anticoagulation during dialysis
LMWH (enoxaparin subcutaneously, 1 mg/kg bid)	Acute DVT/PE	Inhibits factor Xa	Overlap with coumadin until INR therapeutic for 2 days; contraindicated in renal insufficiency
Warfarin	Acute or chronic DVT/PE	Inhibits vitamin K-dependent clotting factors (II, VII, IX, X)*	Monitor for drug interactions
tPa	Hemodynamic compromise attributable to PE	Binds fibrin; potentiates fibrinolysis by fibrinogen degradation	Immediate onset and elimination; hemorrhage concern

(Continued on following page)

SUMMARY OF ACUTE AND SHORT-TERM MANAGEMENT OF VTE *(Continued)*

Treatment	Indications	Primary Mechanism	Comments
IVC filter	High risk for recurrent VTE in patients with low cardiopulmonary reserve; contraindication to anticoagulation: recurrent VTE despite appropriate anticoagulation	Inhibits clot migration from lower extremities to lung	Not indicated in VTE secondary to upper extremity DVT

*Adapted from references 22 and 35

SUMMARY OF LONG-TERM MANAGEMENT FOR VTE

DVT/PE Event	Cause of VTE/ Risk Factor	Length of Treatment
First	Reversible cause (trauma, catheter, immobilization, etc.)	3–6 months or until inciting cause reversed
First	Idiopathic	At least 6 months
First	Cancer or thrombophilia*	At least 12–24 months (individualize to patient)
Second	Reversible cause	Unclear evidence but at least 12 months
Second	Cancer or thrombophilia*	Indefinite (individualize to patient and consider lifelong therapy)
Third	Any	Indefinite/lifelong

*Thrombophilia: deficiencies or insufficiencies of factor V, prothrombin, protein C, S, antithrombin, etc. (adapted from references 35 and 36)

Inpatient Prophylaxis for VTE

SUMMARY OF APPROPRIATE DVT/PE PROPHYLAXIS FOR INPATIENTS

Risk Profile	Patient Profile	Primary Method	Alternative
Low or none	Low-risk ambulatory surgical or medical patient without underlying risk factors	Ambulation	PCD/CS LDUH
Mild	Long-term ambulatory medical in-patient; pregnancy; nursing home patient	LDUH	LMWH PCD/CS
Moderate	Abd, chest, gyn, neurosurgery† (not cancer associated); high-risk medical inpatient or with underlying risk factors‡	LMWH*	LDUH PCD
High	High-risk surgery (orthopedic); hip fracture; multitrauma	LMWH ± PCDs*	Warfarin with INR 2–3, fondaparinux
Very high	Total hip replacement; malignancy-associated surgery	LMWH × 4 or more weeks*	Warfarin with INR 2–3, fondaparinux

*Anticoagulation started within 12 hours postoperation and continued for a minimum of 7–10 d

†In neurosurgical patients, anticoagulation should be started after a 48-hour bridging period with PCDs

‡Includes medical patients with cardiovascular, pulmonary, neurological disease

PCD = pneumatic compression device, CS = compression stockings, LDUH = low-dose unfractionated heparin

Adapted from references 35, 37, and 38



Patient Care Warnings

- Pregnant patients with VTE warrant cautious work-up and treatment
- Start anticoagulation in any patient with a “high” pretest clinical probability before obtaining a confirmatory test as long as there is no contraindication to systemic anticoagulation

References

- ③ 1. Moser KM. Venous thromboembolism. *Am Rev Respir Dis* 1990;141:235-49.
- ③ 2. Weinmann EE, Salzman EW. Deep-vein thrombosis. *N Engl J Med* 1994;331:1630.
- ② 3. Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. *N Engl J Med* 1992;326:1240.
- ② 4. Dismuke SE, Wagner EH. Pulmonary embolism as a cause of death: The changing mortality in hospitalized patients. *J Am Med Assoc* 1986;255:2039.
- ② 5. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979-1998: An analysis using multiple-cause mortality data. *Arch Intern Med* 2003;163:1711-17.
- ② 6. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: Clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353:1386-89.
- ① 7. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *J Am Med Assoc* 1990;263:2753-59.
- ② 8. Rosendaal FR. Venous thrombosis: A multicausal disease. *Lancet* 1999;353:1167-73.
- ② 9. Heit JA, Melton LJ, Lohse CM, et al. Incidence of venous thromboembolism in hospitalized patients vs. community residents. *Mayo Clin Proc* 2001;76:1102.
- ② 10. Stein PD, Saltzman HA, Weg JG. Clinical characteristics of patients with acute pulmonary embolism. *Am J Cardiol* 1991;68:1723.
- ② 11. Girard P, Decousus M, Laporte S, et al. Diagnosis of pulmonary embolism in patients with proximal deep vein

- thrombosis: Specificity of symptoms and perfusion defects at baseline and during anticoagulant therapy. *Am J Respir Crit Care Med* 2001;164:1033.
- ③ 12. Horlander KT, Leeper KV. Troponin levels as a guide to treatment of pulmonary embolism. *Cur Opin Pulm Med* 2003;9:374.
 - ② 13. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: A systematic review. *Ann Intern Med* 2004;140:589.
 - ③ 14. The American Thoracic Society. The diagnostic approach to acute venous thromboembolism: Clinical practice guideline. *Am J Respir Crit Care Med* 1999;160:1043.
 - ② 15. Stein PD, Terrin ML, Hales CA, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no preexisting cardiac or pulmonary disease. *Chest* 1991;100:598-603.
 - ③ 16. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. *Ann Intern Med* 1998;129:1044-49.
 - ② 17. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: A systematic review. *Ann Intern Med* 2000;132:227.
 - ③ 18. Fedullo PF, Tapson VF. The evaluation of suspected pulmonary embolism. *N Engl J Med* 2003;349:1247.
 - ② 19. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998;129:997-1005.
 - ② 20. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patient probability of pulmonary embolism: Increasing the models utility with the SimpliRED D-Dimer. *Thromb Haemost* 2000;83:416.
 - ② 21. Douketis JD, Kearon C, Bates S, et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *J Am Med Assoc* 1998;279:458-62.
 - ③ 22. Buller HR, Agnelli G, Hull R, et al. Antithrombotic therapy for venous thromboembolic disease: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:401S.
 - ② 23. Hull RD, Raskob GE, Brant RF, et al. The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy. *Arch Intern Med* 1997;157:2317.
 - ① 24. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: A metaanalysis of randomized, controlled trials. *Ann Intern Med* 2004;140:175-83.
 - ③ 25. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119:8S.

- ③ 26. Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2001;119:176S.
- ② 27. Kreit JW. The impact of right ventricular dysfunction on the prognosis and treatment of normotensive patients with pulmonary embolism. *Chest* 2004;125:1539-45.
- ② 28. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation* 2000;101:2817.
- ③ 29. Davidson BL, Lensing AW. Should echocardiography of the right ventricle help determine who receives thrombolysis for pulmonary embolism? *Chest* 2001;120:6.
- ③ 30. Goldhaber SZ. Echocardiography in the management of pulmonary embolism. *Ann Intern Med* 2002;136:691.
- ① 31. Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347:1143-50.
- ③ 32. Becker DM, Philbrick JT, Selby JB. Inferior vena cava filters: Indications, safety, effectiveness. *Arch Intern Med* 1992;152:1985.
- ② 33. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med* 1998;338:409.
- ③ 34. Joels CS, Sing RF, Heniford BT. Complications of inferior vena cava filters. *Am J Surg* 2003;69:654.
- ③ 35. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001;119:132S.
- ③ 36. Task Force on Pulmonary Embolism, European Society of Cardiology. Guidelines on diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2000;21:1301.
- ① 37. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: A meta-analysis of randomised trials. *Lancet* 2001;358:9.
- ③ 38. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002;346:975.

MECHANICAL VENTILATION

Definition, Etiology, and Epidemiology

- Mechanical ventilation delivers positive pressure, oxygen-enriched breaths to patients with respiratory failure

- Two types of respiratory failure¹
 - Ventilatory failure: $\text{PaO}_2 > 45$ mm Hg
 - Normal lungs: A-a O_2 gradient < 20 mm Hg
 - Abnormal lungs: A-a O_2 gradient > 20 mm Hg
- Oxygenation failure: low PaO_2 , Paco_2 usually low

CAUSES OF RESPIRATORY FAILURE

Oxygenation Failure	Ventilatory Failure
Low inspired O_2	Increased CO_2 production: fever, sepsis, acidosis, carbohydrate load
Hypoventilation	Increased dead space: pulmonary embolism (PE), chest wall disorders, chronic obstructive pulmonary disease (COPD), asthma
Shunt: alveolar collapse, pneumonia, pulmonary edema, right to left cardiac shunt, intrapulmonary shunt	Central hypoventilation: drugs, brainstem stroke, obesity, hypoventilation syndrome
V/Q mismatch: PE, pneumonia, COPD, asthma	Neuromuscular disorders: myasthenia gravis, Guillain-Barré, amyotrophic lateral sclerosis, polyneuropathy, electrolyte abnormalities (e.g., hypophosphatemia), muscular dystrophy
Diffusion impairment: interstitial lung disease	
Anemia	
Low cardiac output	

Pearls of the Physical Examination

- Signs of respiratory failure: tachypnea with respiratory rate > 30 , rapid shallow breathing, use of accessory muscles, paradoxical abdominal muscle movement, cyanosis, nasal flaring, diaphoresis, conversational dyspnea
- Clues to etiology:

- Rhonchi, egophony, dullness to percussion: may indicate pneumonia or effusion
- Wheezing or lack of air movement: may indicate COPD or asthma exacerbation
- Altered mental status: may indicate severe hypoxia or hypercapnia

Diagnostic Studies and Laboratory Values

- Arterial blood gas: evaluate acid-base status, hypoxia, hypercapnia
- Serum chemistries: monitor serum bicarbonate for signs of chronic respiratory acidosis (compensation for a respiratory acidosis)
- Chest x-ray: look for etiology of respiratory distress: pneumonia, pulmonary edema

Guide to Acute Management

- Indications for intubation²
 - Respiratory failure: hypoxemia or acidosis
 - Respiratory distress: muscle fatigue
 - Neuromuscular disorders
 - Airway protection
- Mallampati's airway score: uvula/soft palate elevation predicts ease of intubation
- Endotracheal (ET) tube management³
 - Attempt oral intubation over nasal intubation unless patient has an oral obstruction or C-spine injury
 - Average size ET tube in an adult is 7.5 Fr. to 8.5 Fr; airway resistance can markedly increase with ET tubes less than 7.0 Fr.
 - After placement, check for bilateral breath sounds, auscultate over stomach, and obtain chest x-ray stat to check positioning
 - Tip of ET tube should be 2-3 cm above the carina on chest x-ray
 - Cuff pressures should be maintained above 18

mm Hg to reduce aspiration but less than 25 mm Hg to reduce the risk of tracheal complications

- Methods of mechanical ventilation
 - Volume-controlled
 - Ventilator delivers a set tidal volume
 - Airway pressures depend on airway resistance and lung compliance
 - Disadvantage: risk for high pressures and possible barotrauma
 - Pressure-controlled
 - Ventilator delivers a set inspiratory pressure
 - Tidal volumes depend on airway resistance and lung compliance
 - Disadvantage: variable tidal volume may lead to hypo- or hyperventilation; time-cycled modes may be uncomfortable for the patient and invite patient-ventilator dyssynchrony

Modes of Mechanical Ventilation^{2,4,5}

Assist Control (AC) Ventilation

- Delivers a minimal number of volume-controlled breaths, some of which may be initiated by patient; any patient-triggered breath delivers a full tidal volume
- Values that can be controlled: FiO_2 , tidal volume, respiratory rate, flow rate, positive end-expiratory pressure (PEEP), sensitivity, flow pattern
- Values that cannot be controlled: peak pressures, direct I:E ratio (but can be adjusted indirectly with flow rate)
- Advantages: decreases work of breathing, delivers a set tidal volume and mandatory minute ventilation
- Disadvantages: peak airway pressure can be difficult to control in a patient with poor lung compliance; can be uncomfortable for the patient and thus require good sedation; tachypnea can lead to respiratory alkalosis; delivered tidal volume will go to

the most compliant areas of the lung, leaving non-compliant areas with possible V/Q mismatches

Synchronized Intermittent Mandatory Ventilation (SIMV)

- Delivers a set number of volume-controlled breaths synchronized to patient's effort but allows patient to breathe spontaneously between breaths without support
- Developed for a patient coming off sedation (weaning)
- Advantages: may observe increased patient comfort as a result of synchrony
- Disadvantages: does not allow patient to rest respiratory muscles; patient must overcome resistance of respiratory circuit during spontaneous breaths, which may lead to fatigue

Pressure Control Ventilation (PCV)

- Delivers a set number of pressure-supported breaths to the airway, with tidal volume depending on pressure and lung mechanics
- Values that can be controlled: PEEP, driving pressure, respiratory rate, I:E ratio
- Values that cannot be controlled: tidal volume, flow rate
- Advantages: allows for increase in mean airway pressures without increasing peak airway pressure; decreases risk of barotrauma
- Disadvantages: very uncomfortable for the patient; requires heavy sedation and often the use of paralytics; tidal volume can be inconsistent; long inspiratory times can result in auto-PEEP

Pressure Support Ventilation (PSV)

- Delivers a preset inspiratory airway pressure for each breath initiated but allows the patient to

determine the rate, flow, and tidal volume based on effort

- The combination of PSV and continuous positive airway pressure (CPAP) is an effective weaning mode
- Advantages: increased comfort for patients who are awake
- Disadvantages: an intact respiratory drive is required; the tidal volume and respiratory rate are determined by the patient and may be inadequate, leading to atelectasis and respiratory acidosis; no backup rate

Continuous Positive Airway Pressure

- Patient breathes spontaneously with a CPAP throughout inspiration and expiration
- Most commonly used as a weaning technique with pressure support
- Advantages: exercises patient's respiratory muscles
- Disadvantages: tidal volume and respiratory rate are determined by patient and may lead to atelectasis and respiratory acidosis

Typical Initial Ventilator Settings

- Mode = AC
- FiO_2 (fraction of inspired air that is oxygen) = 100%
- V_T (tidal volume) = 6-10 mL/kg (depending on reason for initiation)
- RR (respiratory rate) = 10-15/min (may be increased with systemic acidosis)
- Inspiratory flow rate = 60 L/min (the higher the inspiratory flow rate, the lower the I-time and higher the E-time)
- PEEP = 0-5 cm H_2O (the positive pressure applied during exhalation helps prevent atelectasis)

Important Definitions⁵

- *Plateau pressure* (static compliance, parenchymal compliance): the airway pressure at the end of inspiration; goal <30
- *Peak inspiratory pressure* (dynamic compliance, airway resistance): the maximum airway pressure at any time during inspiration; goal <40
- *Dynamic compliance*: the change in volume required to overcome airway resistance and elasticity of the lungs and chest wall (V_t/P_{peak})
- *Static compliance*: the distensibility of the lungs and chest wall (V_t/P_{plateau}); normal value >90 mL/cm H₂O; normal in intubated patients ~50-70 mL/cm H₂O
- *Minute ventilation*: tidal volume multiplied by respiratory rate; goal is highly variable depending on disease state and acid-base balance

Disease-Specific Strategies^{4,5}

Severe Obstruction – COPD or Asthma Exacerbation

- Ventilate with lower lung volumes and lower plateau pressures and allow a slightly higher Paco_2 (permissive hypercapnea)
- Set a high inspiratory flow time (100 L/min) equal to I:E of at least 1:8
- Decrease respiratory rate to 7-8 (permissive hypercapnea)
- Set tidal volume to ~8 mL/kg
- Sedate patient well to decrease pressures
- Aggressive treatment of airflow obstruction with appropriate therapy

Acute Respiratory Distress Syndrome (ARDS)

- Difficulty is often with oxygenating patient
- Set high PEEP 10-15 cm; may prevent microatelectasis
- Set lower tidal volumes (6 mL/kg): limits high air-

way pressures and alveolar overdistention; improves mortality⁶

- Consider prone positioning: thought to decrease V/Q mismatching
- Treat underlying cause
- Steroids and fluid management controversial
- Good supportive care is essential

Noninvasive Ventilation⁷

Methods of Delivery (Using Nasal or Face Mask)

- Volume-controlled ventilator
 - Set tidal volume of 4-8 mL/kg with inspiration
- Pressure-controlled ventilator
 - Deliver a set pressure with inspiration (typically 8-20 cm H₂O)
 - Set PEEP (typically 0-6 cm H₂O)
- Bi-level positive airway pressure (BiPAP)
 - Provides inspiratory and expiratory support pressures that are delivered when breathing efforts are sensed (typically, an inspiratory pressure of 6-14 cm H₂O, expiratory pressure 3-5 cm H₂O)
- CPAP
 - Provides a single flow of continuous positive pressure (typically set at 5-12 cm H₂O)

Indications for Use of Noninvasive Ventilation

- Acute respiratory failure with stable blood pressure, clear mental status
- Chronic respiratory failure from COPD, neuromuscular disorders, sleep apnea

Contraindications to Noninvasive Ventilation

- Hemodynamic instability
- Impaired mental status
- Risk of aspiration
- Upper gastrointestinal bleeding
- Controversial in acute myocardial infarction

Weaning From the Ventilator^{1,2,4,5,8}

Weaning Parameters (General Guidelines)

- Reason for intubation is resolved or markedly improved
- Mental status: alert and following commands; minimal secretions
- $Pao_2 > 60$ mm Hg with $Fio_2 \leq 40\%$
- Vital capacity > 10 mL/kg; negative inspiratory force > -30 cm H_2O
- Tidal volume > 5 mL/kg; static compliance > 30 mL/cm H_2O
- Minute ventilation $< 10-12$ L/min
- Rapid shallow breathing index (RR/TV) < 100 breaths/min/L; sensitive and specific for determining likelihood of successful extubation

METHODS OF WEANING

Mode	Advantages	Disadvantages
T piece	• Patient does all work of breathing • Used for patients who have been intubated for brief period • Trial for 30-60 min; if no signs of fatigue, extubation likely to be successful • Can be tried once daily or intermittently	• No ability to monitor patient's tidal volumes or pressures
Pressure support (PS) $\pm$ CPAP SIMV	• Comfortable for patient • Can gradually decrease PS • Machine-delivered breaths may prevent atelectasis • Rate of machine-delivered breaths can gradually be withdrawn • Can be used with PS to decrease resistance of tubing	• Can lead to respiratory muscle fatigue • Delays weaning from the ventilator

- The optimal weaning method is unclear; two well-designed trials comparing PS and T-piece methods showed conflicting results,^{9,10} but both revealed that SIMV was an inferior weaning method
- Prior to extubation, check for cuff leak (air leak around cuff when cuff pressure released); absence of cuff leak may indicate laryngeal edema

Troubleshooting the Ventilated Patient^{4,5}

Poor Oxygenation

- Check for bilateral breath sounds and tracheal shift; consider pneumothorax
- Deep suction for mucus plugs; check ET tube for cuff leak
- Get chest x-ray stat; patient may have developed ARDS, pulmonary edema, mucous plug, or pneumothorax
- Increase FiO_2 to 100%, and increase PEEP as needed
- Manually ventilate patient, if necessary
- Try prone positioning or recruiting maneuvers

Respiratory Acidosis

- Check ventilator mode: if patient not on A/C, then patient may be tiring
- Check tidal volume
 - If decreased: check for cuff leak, pneumothorax, mucous plug, pulmonary edema, auto-PEEP
 - If stable: check for signs of sepsis, hypovolemia, increased dead space, increased carbohydrate load in diet

Complications of Mechanical Ventilation²

- Barotrauma: alveolar damage, pneumothorax
- Oxygen toxicity at $\text{FiO}_2 > 60\%$
- Ventilator-associated pneumonia
- Sinusitis
- Atrophy of respiratory muscles

- Tracheomalacia, tracheal stenosis
- Auto-PEEP: gas trapping due to incomplete exhalation by patient
- Decreased cardiac output, hypotension
- Thromboembolism
- Malnutrition

References

- ③ 1. Marino PL. The ICU Book, 2nd ed. Baltimore, Lippincott Williams & Wilkins, 1998:339-484.
- ③ 2. Tobin MJ. Mechanical ventilation: Current concepts. *N Engl J Med* 1994;330:1056-61.
- ③ 3. Hyzy RC. Endotracheal tube management. 2004. www.uptodate.com.
- ③ 4. Gammons RB, Shin MS, Groves RH Jr, et al. Mechanical ventilation: A review for the internist. *Am J Med* 1995;99:553-62.
- ③ 5. Chan ED, Winston BW, Terada LS, et al. *Bedside Critical Care Manual*, 2nd ed. Philadelphia, Hanley & Belfus, 2002:1-20.
- ③ 6. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-1308.
- ③ 7. Hillberg RE, Johnson DC. Noninvasive ventilation. *N Engl J Med* 1997;337:1746-52.
- ③ 8. Tobin MJ. Advances in mechanical ventilation. *N Engl J Med* 2001;344:1986-96.
- ① 9. Esteban A, Frutos R, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995;332:345-50.
- ① 10. Brochard L, Rass A, Benito S, et al. Comparison of three methods of gradual withdrawing from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994;150:896-903.

PLEURAL EFFUSIONS

Definition, Etiology, and Epidemiology

- Abnormal collection of fluid within the pleural space¹
- Most common etiologies²
 - Congestive heart failure (CHF)
 - Bacterial pneumonia (parapneumonic effusion)

- Malignancy
- Pulmonary embolus
- Cirrhosis with ascites (usually right-sided effusion)
- Pancreatitis
- Collagen vascular disease
- Tuberculosis (TB)
- Incidence¹
 - Affects approximately 1.3 million people per year in the United States
 - Affects approximately 320 people per 100,000 worldwide

Pearls of the Physical Examination³

- Diminished or absent breath sounds, dullness on percussion, absence of fremitus in the area of the effusion
- May note egophony with consolidation of adjacent lung
- Clues to the underlying cause
 - Elevated jugular venous pressure and edema with CHF
 - Tachycardia with pulmonary embolism
 - Fever with pneumonia (empyema, complicated parapneumonic effusion)
 - Lymphadenopathy with malignancy or granulomatous disease
 - Ascites with cirrhosis
 - Abdominal pain with pancreatitis
 - Anasarca with hypoalbuminemia

Diagnostic Studies and Laboratory Values

Radiology Studies⁴

- Posteroanterior/lateral chest x-ray
 - Typically can detect effusion when >150 mL of fluid has accumulated in the pleural space
 - Unilateral left-sided effusions: esophageal rupture,

splenic abscess or infarct, pancreatic disease, pericardial disease

- Unilateral right-sided effusions: CHF, cirrhosis, hepatic abscess, Meigs' syndrome
- Decubitus chest x-ray
 - Used to confirm the presence of a layering effusion and to evaluate underlying lung parenchyma (therefore, should get bilateral decubitus films)
 - If effusion layers >10 mm and detectable on physical examination, proceed with bedside thoracentesis
 - If effusion partially layers, ultrasound-guided thoracentesis should be considered
- Ultrasound
 - Aids in the identification of loculated effusions and provides guidance for thoracentesis
 - No data to indicate that ultrasound guidance decreases incidence of pneumothorax
- Chest computed tomography
 - Distinguishes consolidation from effusion
 - Aids in visualization of loculations of pleural fluid
 - Identifies masses and associated lymphadenopathy
 - May allow visualization of underlying lung parenchyma
 - Distinguishes uncomplicated from complicated parapneumonic effusions: contrasted study may demonstrate pleural enhancement

Laboratory Studies

- Serum: lactate dehydrogenase (LDH), total protein, albumin
- Pleural fluid: pH, LDH, total protein, glucose, cell count, Gram's stain and culture, amylase, triglycerides
- Additional studies as dictated by history or examination

Evaluating Pleural Fluid (Transudate vs Exudate)

- Light's criteria² for exudative effusion (one of the following):
 - Pleural fluid protein to serum protein ratio >0.5
 - Pleural fluid LDH to serum LDH >0.6
 - Pleural fluid LDH $>2/3$ the upper limit of normal for serum LDH
- Other criteria suggesting exudative effusion²
 - Difference in serum albumin to pleural fluid albumin <1.2 g/dL
 - Ratio of pleural fluid cholesterol to serum cholesterol >0.3

CLUES IN THE PLEURAL FLUID^{1,2,5}

Gross appearance	• Clear serous: hydrothorax, often transudative • Red/bloody: hemothorax (hemocrit in fluid to serum >0.5) • Milky/white: chylothorax (milky white 50% of the time) • Purulent material: empyema • Yellow fluid, smelling of ammonia: urinothorax • Brown, foul-smelling fluid: amebic liver abscess, ruptured esophagus
Cell count	• >50 K: likely complicated parapneumonic effusion • <5 K: likely TB or malignancy
Cell types	• Neutrophil predominance: acute inflammation, often infection • Lymphocyte predominance (85%-95%): malignancy (lymphoma), TB, sarcoidosis, rheumatoid pleurisy, chylothorax, yellow nail syndrome • Eosinophilia ($>10\%$): blood or air in the pleural space, fungal infection, parasitic disease, pulmonary infarction • Mesothelial cells: if $>5\%$, unlikely to be TB

(Continued on following page)

CLUES IN THE PLEURAL FLUID^{1,2,5} (Continued)

Glucose	• Decreased in rheumatoid pleurisy (<30), bacterial infections, malignancy
pH	• <7.20: consider complicated effusion, rheumatoid pleurisy, or cancer • <7.0: consider esophageal rupture, urinothorax
Amylase	• Increased in esophageal rupture, pancreatitis, malignancy
Triglycerides	• >110 suggests chylothorax
Protein	• >5.0 g/dL suggestive of TB
Antinuclear antibody (ANA), rheumatoid factor (RF)	• ANA >1.0: lupus pleurisy • RF >1:320: rheumatoid pleurisy
Gram's stain and culture	• Positive Gram's stain: complicated parapneumonic effusion
Adenosine deaminase (ADA) and interferon (IFN) gamma	• ADA >47: very sensitive for TB, not specific • IFN gamma >3.7 U/mL: good specificity for TB
Cytology	• Can identify malignant cells • Add flow cytometry if suspicion for lymphoma

ETIOLOGY BASED ON TYPE OF EFFUSION^{1,2,5}

Transudative	Exudative	Transudative or Exudative
• CHF • Cirrhosis • Nephrotic syndrome • Superior vena cava obstruction • Urinothorax • Peritoneal dialysis	• Infections: parapneumonic effusion, tuberculous pleuritis, hepatic abscess • Gastrointestinal disease: pancreatitis, pancreatic pseudocysts, esophageal perforation, intra-abdominal abscess, biliary tract obstruction	• Pulmonary embolism • Hypothyroidism • Malignancy

ETIOLOGY BASED ON TYPE OF EFFUSION^{1,2,5} (Continued)

Transudative	Exudative	Transudative or Exudative
• Constrictive pericarditis	• Connective tissue disease: rheumatoid pleurisy, lupus pleuritis, Churg-Strauss disease, Wegener's granulomatosis, Sjögren's syndrome • Malignancy (chylothorax, hemothorax): carcinoma, lymphoma, mesothelioma, multiple myeloma, Waldenström's, disease, leukemia • Cardiovascular disease: Dressler's syndrome, post-coronary artery bypass graft • Meigs' syndrome • Asbestosis • Yellow nail syndrome • Radiation-induced • Trapped lung • Uremia • Drugs: nitrofurantoin, dantrolene, methysergide, bromocriptine, procarbazine, amiodarone	

- Infectious causes of pleural effusions⁵
 - Bacterial: most common organisms are *Streptococcus pneumoniae* and *Staphylococcus aureus*
 - *Mycobacterium*: typically unilateral with small to moderate effusion, ipsilateral hilar adenopathy
 - Actinomycosis: characteristic infiltrates extending to adjacent lobes through intralobular fissures, chest-wall abscesses, draining sinus tracts
 - Nocardiosis: consider in immunosuppressed patients
 - Fungal infections: aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis (rare)

- Viral/atypicals: mycoplasma, hepatitis, hantavirus, respiratory virus, influenza
- Parasitic: amebiasis, echinococcosis, paragonimiasis
- HIV-associated effusions: Kaposi's, lymphoma, TB, *Pneumocystis carinii* pneumonia (uncommon)

Guide to Acute Management^{2,3,5}

- New unilateral pleural effusions should be sampled for diagnosis
- Bilateral effusions in a patient with known CHF without a fever can be observed with a trial of diuresis; if the effusions do not resolve with aggressive diuresis for 2-3 days, the effusion should be sampled for diagnostic studies
- Partially layering effusions should be tapped with the aid of ultrasound guidance
- Management based on treating the underlying cause
- Parapneumonic effusions
 - Remove all fluid with initial thoracentesis
 - If uncomplicated, treat with antibiotics
 - If complicated (pH <7.20, LDH >3 × the upper limits of normal, glucose <60, positive Gram's stain, or positive culture) or empyema (gross purulence), treat with chest tube placement or video-assisted thoracoscopy
- Malignant effusions: may require serial therapeutic thoracenteses, pleurex catheter placement, or chest tube placement with pleurodesis; low pH and low glucose are poor prognostic indicators
- Chylothorax: should not be treated with long-term chest tube drainage as this may lead to malnutrition
- Pleural biopsy: may be needed to establish a diagnosis of TB
- Bronchoscopy: rarely helpful in identifying etiology

of effusion unless associated with endobronchial mass, which can be biopsied

- Thoracoscopy: allows for complete drainage of the pleural space, lysis of adhesions, biopsy of the pleural space and lungs, and aids in pleurodesis
- Pleurodesis: often used with malignant effusions to prevent reaccumulation; agents (talc, bleomycin, doxycycline) can be given through chest tube or thoracoscopy to induce fibrosis and pleural adhesion



Patient Care Warnings

- A patient presenting with pneumonia and an effusion on the initial chest x-ray has a complicated parapneumonic effusion (empyema) until proven otherwise
- No more than 1500 mL of fluid should be drained in one setting due to risk of reexpansion pulmonary edema
- If patient has shortness of breath at rest or hypoxemia, therapeutic thoracentesis may be necessary
- Urinothorax is the only transudative effusion with a low pH

References

- ③ 1. Abrahamian FM. Pleural effusion. 2001. www.Emedicine.com
- ③ 2. Light RW. Pleural effusion. *N Engl J Med* 2002;346:1971-77.
- ③ 3. Bordow RA., Morris T, Ries AL. *Manual of Clinical Problems in Pulmonary Medicine*, 5th ed. 2001:61-66.
- ③ 4. Stark P. Imaging of pleural effusions. 2004. www.uptodate.com
- ③ 5. Light RW, Broaddus C. Pleural effusion. In *Textbook of Respiratory Medicine*, 3rd ed. 2000:2013-41.

INTERSTITIAL LUNG DISEASE

Definition, Etiology, and Epidemiology

- Inflammatory-fibrotic infiltration of the alveolar walls, resulting in stiff, noncompliant lungs and decreased lung volumes
- Includes more than 100 entities that injure the alveoli and small airways, producing a disease with similar clinical, radiographic, and physiological features¹
- Clinical classification²
 - Occupational/environmental exposures
 - Inorganic dust: silica, asbestosis, talc, coal, beryllium, tin, iron
 - Organic dust (hypersensitivity pneumonitis): bird breeder's lung, farmer's lung, grain handler's lung, humidifier lung
 - Drug/treatment-induced
 - Nitrofurantoin, amiodarone, tocainide, bleomycin, busulfan, methotrexate, cyclophosphamide, chlorambucil, cocaine, heroin, oxygen, radiation
 - Connective tissue diseases
 - Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, polymyositis/dermatomyositis, Sjögren's syndrome
 - Sarcoidosis and other granulomatous diseases
 - Idiopathic interstitial pneumonia (IIP): modified Katzenstein and Meyers classification^{3,4}
 - Idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonitis (DIP), respiratory bronchiolitis interstitial lung disease (RBILD), lymphocytic interstitial pneumonitis (LIP), cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonitis (NSIP), acute interstitial pneumonia (AIP or Hamman-Rich syndrome)
 - Other primary causes

- Langerhans' cell histiocytosis, lymphangitic carcinomatosis, bronchoalveolar carcinoma, pulmonary lymphoma, lymphangiomyomatosis (LAM), acute respiratory distress syndrome, alveolar proteinosis, Goodpasture's syndrome, idiopathic pulmonary hemosiderosis, Hermansky-Pudlak syndrome, Gaucher's disease, Niemann-Pick disease, tuberous sclerosis (TS), neurofibromatosis type 1 (NF1), bone marrow transplantation, postinfectious
- Incidence: 31.5/100,000 per year in men; 26.1/100,000 per year in women⁵
- Prevalence: 80.9/100,000 in men, 67.2 in 100,000 in women⁵
- IPF is the most common form of ILD

Pearls of the History and Physical Examination

History

- Progressive dyspnea (most common)
- Nonproductive cough (common in IPF, sarcoidosis, hypersensitivity pneumonitis, eosinophilic granuloma, lymphangitic carcinomatosis)
- Chest pain: uncommon overall but occurs in sarcoid, RA, SLE, drug-related ILD
- Hemoptysis: uncommon overall but occurs in alveolar hemorrhage syndromes, LAM
- Occupational/environmental exposures
- Drugs: medications and illicit
- Radiation exposure
- Tobacco use (Langerhans' cell histiocytosis, lung cancer, some idiopathic interstitial pneumonias)
- Family history (familial IPF, TS, NF1, LAM, sarcoidosis, Niemann-Pick disease, Gaucher's disease, Hermansky-Pudlak syndrome)
- Other systemic symptoms may point toward a specific causative disease (i.e., arthritis, Raynaud's disease, heliotrope rash, malar rash, muscle weakness)

Physical Examination

- Bibasilar, late inspiratory dry crackles
- Clubbing (present in 80% of patients with IPF)
- Evidence of pulmonary hypertension/cor pulmonale: elevated jugular venous pressure, ascites, loud P₂, peripheral edema

Diagnostic Studies and Laboratory Values

Chest X-Ray^{1,2}

- 10% of symptomatic patients diagnosed with ILD have a normal chest x-ray
- Pattern may be alveolar-filling, interstitial infiltrates, or mixed
- Alveolar-filling pattern: alveolar proteinosis, alveolar cell carcinoma, bronchioloalveolar metastases, pulmonary lymphoma, LIP, DIP, diffuse alveolar hemorrhage syndromes, sarcoidosis, eosinophilic pneumonia, mineral oil aspiration
- Alveolar-filling pattern with hilar or mediastinal lymphadenopathy: sarcoidosis, lymphoma, lymphocytic interstitial pneumonia, idiopathic pulmonary hemosiderosis

RADIOGRAPHIC FEATURES OF THE INTERSTITIAL LUNG DISEASES*

Feature	Diseases
Kerley B lines	Lymphangitic carcinomatosis, sarcoidosis, LAM, lymphoma, amyloidosis, left heart failure
Radiographic homeycomb lung	IPF, CTD, asbestosis, drug-induced ILD, chronic aspiration pneumonia, hemosiderosis, Hermansky-Pudlak syndrome, alveolar proteinosis, hypersensitivity pneumonitis (HP)

RADIOGRAPHIC FEATURES OF THE INTERSTITIAL LUNG DISEASES* (*Continued*)

Feature	Diseases
Upper zone predominance	Radiation, NF1, sarcoidosis, Langerhans' cell histiocytosis, silicosis, chronic HP, chronic eosinophilic pneumonia, nodular RA, berylliosis, drug-induced ILD
Lymphadenopathy	Sarcoidosis, lymphoma, lymphangitic carcinomatosis, LIP, berylliosis, amyloidosis, Gaucher's disease
Pleural disease	Lymphangitic carcinomatosis, CTD, asbestosis, LAM, drug-induced ILD
Eggshell calcification of lymph nodes	Silicosis, sarcoidosis, radiation
Increased lung volumes	LAM, chronic eosinophilic granuloma, TS, NF1
Pneumothorax	LAM, TS, NF1, chronic eosinophilic granuloma

*Adapted from reference 1

High-Resolution Computed Tomography (HRCT) Scan

- Improved sensitivity over chest x-ray alone
- Disease distribution as defined by HRCT (i.e., lung zone predominance: peripheral vs. central, upper vs. lower) and pattern (reticular, nodular, "ground glass," consolidation) can help narrow differential⁶
- Amount of inflammation (ground glass opacification) versus fibrosis (dense lines) provides important prognostic information

Laboratory Studies

- Arterial blood gas (ABG): may be normal or show hypoxia and/or respiratory alkalosis; exercise ABG or oximetry may be useful to show exercise-induced hypoxia⁶
- Serum markers for certain systemic diseases may

be helpful (RF, ANA, SCL-70, ANCA, anti-Jo-1 antibody, anti-RNP) if concern for connective tissue or autoimmune disease

- Pulmonary function tests
 - Spirometry, lung volumes, and diffusion capacity: typical pattern is restrictive with decreased total lung capacity, functional residual capacity, and residual volume; diffusing capacity of the lung for carbon monoxide (DLCO) is typically decreased⁶
 - Can be useful to verify presence of disease in patients with normal chest x-ray results
 - Can be useful to monitor disease progression and response to therapy²
- Bronchoalveolar lavage to assess for reactive/inflammatory cells (depending on HRCT pattern)
- Lung biopsy: excludes sarcoidosis, infections, and cancer; rarely diagnostic due to small sample size

Treatment

- Chronic therapy depends on etiology of the ILD
- Antigen/drug avoidance in the case of hypersensitivity pneumonitis or drug-induced ILD, exposure avoidance for pneumoconioses
- Corticosteroids may be indicated in certain cases – sarcoidosis,⁷ desquamative interstitial pneumonia, lymphocytic interstitial pneumonia, cryptogenic organizing pneumonia, IPF (although no clear benefit established),^{5,8} connective tissue diseases, HP⁹
- Cytotoxic agents (azathioprine or cyclophosphamide) may be indicated in certain cases, but little evidence available to suggest benefit
- Oxygen

- Antibiotics/antiviral medications if indicated for superimposed infection



Patient Care Warnings

- A normal chest x-ray does not exclude ILD
- The most sensitive historical finding in a patient with ILD is exertional dyspnea
- Exercise-induced hypoxemia is a simple and sensitive diagnostic test

References

- ③ 1. King TE Jr. Principles of and approach to the patient with interstitial lung disease. In Murray JF, Nadel JA (eds). Textbook of Respiratory Medicine, 3rd ed. Philadelphia, WB Saunders, 2000:1649.
- ③ 2. Schwarz MI. Approach to the understanding, diagnosis, and management of interstitial lung disease. In Schwarz MI, King TE. Interstitial Lung Disease, 3rd ed. Hamilton, BC, Decker, 1998:3.
- ③ 3. American Thoracic Society. Idiopathic pulmonary fibrosis: Diagnosis and treatment. International consensus statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161:646-64.
- ③ 4. Collard HR, King TE Jr. Demystifying idiopathic interstitial pneumonia. Arch Intern Med 2003;163:17-29.
- ③ 5. Coultas DB, Zumwalt RE, Black WC, et al. The epidemiology of interstitial lung disease. Am J Respir Crit Care Med 1994;150:967.
- ③ 6. King TE Jr. Approach to the adult with interstitial lung disease. 2004. www.uptodate.com
- ③ 7. American Thoracic Society. ATS guidelines: Statement on sarcoidosis. Am J Respir Crit Care Med 1999;160:736.
- ③ 8. Mapel DW, Samet JM, Coultas DB. Corticosteroids and the treatment of idiopathic pulmonary fibrosis: Past, present, and future. Chest 1996;110:1058.
- ② 9. Monkare S. Influence of corticosteroid treatment on the course of farmer's lung. Eur J Respir Dis 1983;64:283.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Definition, Etiology, and Epidemiology

- ARDS is an inflammation-induced increase in capillary and alveolar permeability causing edema, diffuse alveolar damage, pulmonary hypertension, and hypoxic respiratory failure
- Diagnostic criteria¹
 - Acute onset
 - Bilateral infiltrates on chest radiograph
 - Stiff, noncompliant lungs (static compliance <30 mL/cm H₂O)
 - Pulmonary capillary wedge pressure (PCWP) of ≤ 18 mm Hg or absence of left atrial hypertension (clinical evidence of congestive heart failure [CHF])
 - $\text{PaO}_2:\text{FiO}_2 \leq 300$ (acute lung injury) versus $\text{PaO}_2:\text{FiO}_2 \leq 200$ (ARDS)

ASSOCIATED CONDITIONS: ARDS USUALLY FOLLOWS INSULT WITHIN 72 HOURS²

Direct Lung Injury	Indirect Lung Injury
Pneumonia	Sepsis
Aspiration	Trauma
Pulmonary contusion	Transfusion-related injury
Fat emboli	Drug overdose
Near drowning	Pancreatitis
Inhalation injury	Tocolytics
Reperfusion pulmonary edema	

- Acute interstitial pneumonia (AIP, Hamman-Rich syndrome): ARDS-like profile with no obvious associated condition

- Incidence² decreased in last decade to 1.5-8.3 per 100,000 population/year in United States
- Risk factors³
 - Age >65 years
 - Presence of chronic lung disease
 - Chronic alcoholism
 - No increased risk based on gender
- Mortality rate estimated to be as high as 30%-50%⁴

Pearls of the Physical Examination

- Depends on the underlying cause
 - Tachypnea, tachycardia, hypotension, fever with sepsis (systemic inflammatory response syndrome [SIRS] criteria)
 - Pulmonary examination with bronchial breath sounds, dependent crackles, rhonchi, or egophony
 - Petechial rash on skin if associated with disseminated intravascular coagulation (DIC) or fat embolism (a rare cause of ARDS)

Diagnostic Studies and Laboratory Values

- Arterial blood gas (ABG): acute respiratory alkalosis with refractory hypoxemia
- Shunt study: after intubation, have patient breathe 100% FiO_2 for 1 hour, then check ABG. If PaO_2 is less than 100 mm Hg, this signifies a shunt of >30% cardiac output ($V/Q = 0$)
- Blood cultures positive in sepsis
- Sepsis: low/normal white blood cell count, positive cultures, disseminated intravascular coagulation (DIC)
- Elevated amylase/lipase with pancreatitis
- Often accompanied by evidence of multisystem organ failure
- Radiological studies²

- Chest x-ray: progression from bilateral interstitial infiltrates to diffuse fluffy alveolar infiltrates; may see air bronchograms; ARDS can be distinguished from CHF by lack of pulmonary venous congestion, Kerley B lines, or cardiomegaly, but distinguishing can be very difficult
- CT chest: alveolar filling, consolidation, and atelectasis primarily in dependent lung zones (heterogeneous distribution), bilateral reticular opacities may be seen in later stages indicating interstitial fibrosis

Guide to Acute Management

- Aggressive search for and treatment of underlying cause
- Mechanical ventilation strategies
 - FiO_2 : goal is $\text{PaO}_2 > 60$ and $\text{FiO}_2 < 0.6$.
 - Tidal volume: lower tidal volume using 6 mL/kg ideal body weight (lung protective ventilation) showed a 22% mortality reduction⁵; the PaCO_2 often rises, and atelectasis may occur with small tidal volumes
 - Positive end-expiratory pressure (PEEP): decreases intrapulmonary shunt by preventing alveolar collapse; titrate PEEP up until FiO_2 is $< 60\%$; combining low tidal volume and high PEEP has resulted in a decreased mortality rate⁶
 - I:E ratio: increased inspiratory time, and thus ratio of inspiratory to expiratory time, can increase mean airway pressure and improve oxygenation
 - High frequency oscillatory ventilation: promising for severe oxygenation problems, but has not shown a long-term survival benefit
- Recruiting maneuvers: high pressure ventilation with continuous positive airway pressure using

30-40 cm H₂O for 20 seconds opens atelectatic lung and increases Pao₂⁷

- Prone positioning: improves overall V/Q ratio and increases Pao₂ in some patients; effective only for first 7 days, but no mortality benefit⁸
- Fluid balance: controversy whether fluid should be restricted to decrease pulmonary edema and improve oxygenation or used liberally to help maintain perfusion; retrospective data seems to support fluid restriction, but prospective data have not been published; due to controversy, an ARDS network study was stopped in 2002⁹
- Pharmacological strategies
 - Steroids: antiinflammatory and may decrease collagen deposition; no mortality benefit and increased infection rate in early phases of ARDS; may be beneficial in later stage (fibroproliferative ARDS)¹⁰
 - Inhaled nitric oxide: vasodilator; temporary improvements in oxygenation but no long-term mortality benefit.
 - Surfactant: decreases alveolar surface tension; beneficial in infants but no mortality benefit in adults; newer preparations are being studied¹¹
 - Activated protein C: inhibits coagulation and inflammation; has a mortality benefit in sepsis but subgroup analysis on ARDS patients not done¹²
 - No proven benefit: ketoconazole,¹³ lisofylline¹⁴



Patient Care Warnings

- Respiratory failure typically occurs within 72 hours of initial lung injury
- Supportive care is key; focus on minimizing complications¹⁵

Complications	Patient Care Approach
Ventilator-associated pneumonia	Head elevation, suctioning, early weaning
Barotrauma	Limit airway and plateau pressures
Hypotension	Limit excessive diuresis and PEEP
Central venous line complications	Careful attention to placement technique, including full barrier protection
Gastrointestinal bleeding	Stress ulcer prophylaxis
Thromboembolism	Sequential compression devices and/or subcutaneous heparin
Excessive sedation	Titrate using sedation assessment scales
Excessive paralysis	Continuous monitoring with train-of-four stimulation; do not use paralytic drugs with corticosteroids
Malnutrition	Initiate tube feeding as soon as possible

References

- ③ 1. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818-24.
- ③ 2. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;342:1334-49.
- ② 3. Hudson LD, Milberg JA, Anardi D, et al. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;151:293-301.
- ② 4. Doyle RL, Szaflarski N, Modin GW, et al. Identification of patients with acute lung injury: Predictors of mortality. *Am J Respir Crit Care Med* 1995;152:1818-24.
- ① 5. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-1308.
- ① 6. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 2000;338:347-54.
- ② 7. Lapinsky SE, Aubin M, Mehta S, et al. Safety and efficacy of a sustained inflation for alveolar recruitment in adults with respiratory failure. *Intensive Care Med* 1999;25:1297-1301.
- ① 8. Gattinoni L, Tognoni G, Pegenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001;345:568-73.

- ② 9. Drazen JM. Controlling research trials. *N Engl J Med* 2003; 348:1377-80.
- ① 10. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome. *JAMA* 1998;280:159-65.
- ③ 11. Lewis JF, Veldhuizen R. The role of exogenous surfactant in the treatment of acute lung injury. *Ann Rev Physiol* 2003; 65:613-42.
- ① 12. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.
- ① 13. ARDS Network. Ketoconazole for the early treatment of acute lung injury and acute respiratory distress syndrome. *J Am Med Assoc* 2000;283:1995-2002.
- ① 14. ARDS Network. Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress. *Crit Care Med* 2002;30:1-6.
- ③ 15. Mortelliti MP, Manning HL. Acute respiratory distress syndrome. *Am Fam Physician* 2002;65:1823-30.

EVALUATION OF HEMOPTYSIS

Definition, Etiology, and Epidemiology¹

- Coughing of blood from the lungs
- Must be differentiated from pseudohemoptysis (bloody sputum from nasopharynx or oropharynx) and hematemesis
- Massive hemoptysis usually refers to >600 mL/d in most studies, but >20-50 mL is considered significant enough to warrant hospitalization
- Oxygen transfer is impaired when 400 mL of blood is present in the alveolar space
- Massive hemoptysis is a medical emergency but accounts for less than 5% of all cases of hemoptysis presenting to the emergency room^{2,3}
- Smaller volumes of hemoptysis may also be life-threatening in patients with diminished cardiopulmonary reserve
- The high-pressure bronchial arteries are the usual source of massive hemoptysis; bleeding can also

arise from pulmonary arteries, bronchial capillaries, and alveolar capillaries

- Etiology (varies by geography and time)⁴
 - Bronchitis (most common cause in United States)³
 - Tuberculosis (TB) (most common worldwide)
 - Bronchiectasis
 - Malignancy
 - Pneumonia
 - Other
 - Infectious: mycetoma, abscess, cystic fibrosis
 - Cardiovascular: mitral stenosis, severe left ventricular failure, aortobronchial fistula, arteriovenous malformations (AVM)
 - Pulmonary embolism or infarction
 - Coagulopathy: anticoagulant therapy, disseminated intravascular coagulation, thrombocytopenia, hemophilia, von Willenbrand's disease
 - Autoimmune diseases/vasculitis: Wegener's syndrome, systemic lupus erythematosus, Goodpasture's syndrome, Behçet's syndrome
 - Iatrogenic
 - Idiopathic
 - Rare causes: catamenial, broncholithiasis
 - The usual causes of massive hemoptysis are cancer, tuberculosis, bronchiectasis, and lung abscess

Pearls of the History and Physical Examination

- Must differentiate massive from submassive hemoptysis
 - Patients with more than 30-50 mL/d should be hospitalized⁵
- History
 - Important clues: age, smoking history, travel, valvular heart disease, trauma, bleeding disorders, pleuritic chest pain and shortness of

breath, hematuria (to suggest a pulmonary-renal syndrome)

- Recurrent hemoptysis: bronchiectasis, catamenial, cancer
- Smoker with weight loss: suggests neoplastic disease
- Less common symptoms: acute onset (pneumonia) or subacute (tuberculosis or nontuberculous mycobacteria, malignancy/lymphoma)
- Physical examination
 - Normal lung examination is the most common finding¹
 - Stridor, wheezing, diffuse crackles, diminished focal breath sounds could point to potential source
 - Cardiac examination: S₃ (congested heart failure) or S₄ (uncontrolled hypertension), diastolic murmur (mitral stenosis)

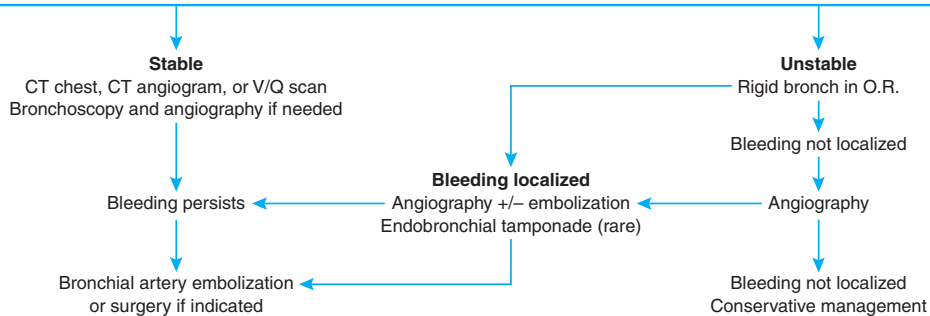
Diagnostic Studies and Laboratory Values

- Presence of hypoxia, severe dyspnea, or hypotension are ominous signs
- Laboratory studies
 - Sputum evaluation
 - Bloody purulent sputum suggests infectious cause
 - Stain for bacteria, acid-fast bacteria
 - Culture for bacteria, mycobacteria, fungal etiology
 - Consider cytology if cancer is suspected
 - Complete blood count with differential for anemia or thrombocytopenia, coagulation studies, serum chemistries
 - Arterial blood gas
 - If diffuse alveolar hemorrhage is suspected, should also check urinalysis with micro, ANA, ANCA, anti-GBM antibodies, complement, and cryoglobulins

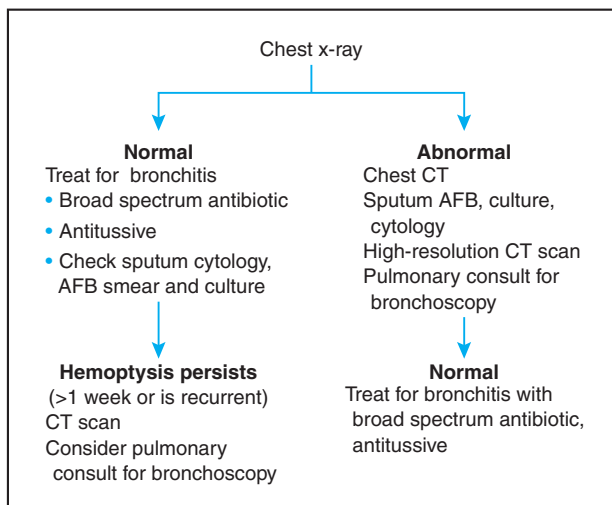
- Posteroanterior/lateral chest x-ray: look for cavitary disease, mass, infiltrate, atelectasis; normal chest x-ray is observed in 20%-40% of patients with hemoptysis⁶; an abnormal x-ray can also help localize the side of bleeding
- Computed tomography (CT): can detect 50% of bleeding sources in patients with normal chest x-ray⁷ and is the preferred study in stable patients with hemoptysis
 - Interstitial, diffuse “ground glass” or consolidation: interstitial lung disease, vasculitis, Goodpasture’s syndrome
 - Focal infiltrate: infectious
 - Cavitary disease: TB, mycetoma, abscess
 - Nodule or mass: malignancy
 - Bronchiectasis
- CT angiography or V/Q scan to look for evidence of thromboembolic disease
- Bronchoscopy: provides direct visualization of bleeding source (see section titled Indications for Emergent Bronchoscopy)
 - Procedure helpful in nonacute settings where biopsy, washings, and brushings can be sent for culture and cytology
- Bronchial arterial angiography/embolization: reserved for persistent bleeding in the acute setting, especially in patients with chronic lung disease, and is the preferred procedure before surgical intervention is attempted⁸

Guide to Acute Management

• Vital signs, O₂ saturation, ABG • Maintain ventilation and oxygenation (intubate if necessary: 8.0Fr or higher for bronchoscopy) • Check CBC, coags, chemistries, type and cross-match for blood, platelets, or plasma	• Fluid resuscitation, blood products as needed • CXR • Consult cardiovascular thoracic surgery, interventional radiology, pulmonology • Consider placing affected side in dependent recumbent position to avoid contralateral aspiration (no proof-ref) • Consider selective lung ventilation with a double-lumen endotracheal tube • Admit/transfer to intensive care unit



Massive hemoptysis (>400 mL/24 hr, or >100 mL/hr). (Adapted from Lordan JL, Gascoigne A, Corris PA. The pulmonary physician in critical care, case 7: Assessment and management of massive hemoptysis. Thorax 2003;58:814-19).



Minor hemoptysis. (Adapted from Johnson JL. Manifestations of hemoptysis: How to manage minor, moderate, and massive bleeding. *Postgrad Med* 2002;112:101-13)



Patient Care Warnings

- Alveolar bleeding may occur with little hemoptysis but may require more aggressive management
- Aortobronchopulmonary fistulas may present with small “sentinel bleeds” that lead rapidly to exsanguination
- Smokers with hemoptysis and normal chest radiographs require bronchoscopy

References

1. Corder R. Hemoptysis. *Emerg Med Clin North Am* 2003;21: 421-35.
2. Lordan JL, Gascoigne A, Corris PA. The pulmonary physician in critical care, case 7: Assessment and management of massive hemoptysis. *Thorax* 2003;58:814-19.

- ② 3. Johnston H, Reisz G. Changing spectrum of hemoptysis: Underlying causes in 148 patients undergoing diagnostic flexible fiberoptic bronchoscopy. *Arch Intern Med* 1989; 149:1666-68.
- ② 4. Fidan A, Ozdogan S, Oruc O, et al. Hemoptysis: A retrospective analysis of 108 cases. *Respir Med* 2002;96:677-80.
- ③ 5. Johnson JL. Manifestations of hemoptysis: How to manage minor, moderate, and massive bleeding. *Postgrad Med* 2002;112:101-13.
- ③ 6. Flower CDR, Jackson JE. The role of radiology in the investigation and management of patients with hemoptysis. *Clin Radiol* 1996;51:391-400.
- ③ 7. Millar AB, Boothroyd AE, Edwards D, et al. The role of computed tomography in the investigation of unexplained hemoptysis. *Respir Med* 1992;86:39-44.
- ③ 8. Haponik EF, Fein A, Chin R. Managing life-threatening hemoptysis: Has anything really changed? *Chest* 2000;118:1431-35.

PULMONARY HYPERTENSION

Definition, Etiology, and Epidemiology

- Exists when the mean pulmonary artery pressure exceeds 25 mm Hg at rest or 30 mm Hg during exercise¹

Secondary Pulmonary Hypertension (SPH)^{2,3}

- Three potential mechanisms:
 - Hypoxemia: leading to pulmonary vasoconstriction
 - Chronic obstructive pulmonary disease (COPD) (most common cause)
 - Obstructive sleep apnea
 - Alveolar hypoventilation from any cause
 - Chronic high altitude exposure
 - Interstitial lung disease (ILD)
 - Reduced surface area of pulmonary vasculature (i.e., vessel obliteration)
 - Pulmonary embolism
 - Collagen vascular disease (systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis)
 - Sickle-cell disease
 - ILD

- Pressure or volume overload of pulmonary circulation
 - Left ventricle dysfunction
 - Valvular heart disease
 - Intracardiac shunt
 - Fibrosing mediastinitis
 - Neoplasm or lymphadenopathy obstructing pulmonary venous flow
 - Pulmonary veno-occlusive disease (rare)
- SPH more common than primary pulmonary hypertension (PPH), although exact prevalence is uncertain
- Males > females; likely related to tobacco use and COPD history
- A third of patients with systemic sclerosis and up to 50% of those with Calcinosis, Raynaud's disease, loss of muscle control of the Esophagus, Sclerodactyly, and Telangiectasia (CREST syndrome) will develop SPH
- Prognosis and reversibility depend on inciting cause

PPH: Diagnosis of Exclusion^{1,4}

- Etiology poorly understood but likely related to:
 - Imbalance between thromboxane and prostacyclin
 - Reduced nitric oxide production
- 1-2 cases per million in the general population¹
- Median lifespan 2.8 years after diagnosis without treatment²
- Female-to-male ratio 2:1
- Classification
 - Familial form: autosomal dominant pattern with genetic anticipation; linked to bone morphogenetic protein receptor, type II (BMPR2)^{4,5}; responsible for ~6% of cases¹
 - Other risk factors: HIV infection, cocaine inhalation or amphetamine use, portal hypertension, diet pills

Pearls of the History and Physical Examination^{1,4,5}

History

- Exertional dyspnea (most common presenting symptom)
- Fatigue, lethargy
- Chest pain, angina
- Syncope (especially with exertion): bad prognostic sign
- Symptoms of right heart failure with advancing disease: peripheral edema, abdominal pain, poor appetite

Physical Examination

- Loud P₂
- Right-sided S₃ or S₄ gallop
- Right ventricular (RV) lift
- Elevated jugular venous pressure
- Tricuspid regurgitation murmur
- Clues to secondary causes: wheezing or clubbing (primary pulmonary disease), left heart murmurs, sclerodactyly or telangiectasias (systemic sclerosis), central cyanosis (right-to-left cardiac shunt)

Diagnostic Studies and Laboratory Values⁶

Transthoracic Echocardiogram (TTE)

- Provides estimates of RV function and size, pulmonary artery pressure, and cardiac output
- Useful to rule out cardiac causes such as valvular heart disease, LV dysfunction, or intracardiac shunts

Right Heart Catheterization

- Invasive but is the gold standard for diagnosis
- Also useful for titrating vasodilator therapy after validating responsiveness to vasodilators

Chest X-Ray

- May see large central pulmonary arteries (PAs) (right descending PA >2 cm supports the diagnosis), enlarged right atrium and right ventricle, signs of pulmonary edema with LV dysfunction or pulmonary veno-occlusive disease

Electrocardiogram

- May see evidence of right ventricle hypertrophy with right-axis deviation, right bundle branch block, and/or P-pulmonale

Ventilation-Perfusion (V/Q) Scan⁷

- Multiple segmental-sized defects observed with chronic thromboembolic disease
- A negative scan essentially rules out pulmonary emboli as a cause

Pulmonary Function Tests

- Used to rule out primary respiratory diseases such as COPD or ILD
- Diffusion capacity of the lung for carbon monoxide is reduced in conditions affecting the pulmonary arteries

Polysomnography or Nocturnal Oximetry

- Used to evaluate for obstructive sleep apnea

Chest Computed Tomography (CT)

- High-resolution scans to evaluate for ILD
- CT angiogram to evaluate for pulmonary emboli

Laboratory Studies

- Arterial blood gas, pulse oximetry: test with exercise if resting results are normal

- Urine toxicology screen (especially for cocaine and amphetamines)
- HIV test
- Liver function tests
- Thyroid function tests: TSH, fT₄
- ESR, ANA, Scl-70 (connective tissue diseases)
- Hepatitis virus serologies

Guide to Acute Management^{8,9}

- Anticoagulation: coumadin with goal International Normalized Ratio (INR) 1.5-2.5; not rigorously tested in clinical trials but recommended due to increased risk of in situ thrombosis observed in postmortem studies¹⁰
- Oxygen supplementation: used for patients with Pao₂ <60 mm Hg at rest, with exercise, or during sleep; goal oxygen saturation >90%
- Diuretics: gently used to decrease right ventricular preload
- Digoxin: no clear data but most useful for coexisting atrial fibrillation
- Vasodilator therapy: primarily used for PPH but may be tried in severe forms of SPH
 - Responders vs. nonresponders determined by infusion of IV prostacyclin, IV adenosine, or inhaled nitric oxide during right heart catheterization: responders have a ≥20% reduction of pulmonary artery pressure or pulmonary vascular resistance
 - Calcium channel blockers (nifedipine or diltiazem): used only in patients who respond to vasodilator challenge and improve to New York Heart Association (NYHA) class I or II categories on therapy, can otherwise cause severe hemodynamic compromise; small percentage of patients have sustained response from this therapy¹¹
 - Prostacyclin (epoprostenol) via continuous IV infusion device

- No large-scale randomized trials, but smaller studies support improved exercise tolerance, decreased pulmonary artery pressure, and improved survival in NYHA III and IV¹²⁻¹⁴
- Some nonresponders may benefit from empiric therapy
- Other experimental prostacyclins: treprostanil by subcutaneous continuous infusion¹⁵; beraprost: orally acting analog^{16,17}; ilioprost: inhaled aerosolized particles^{18,19}
- Endothelin-1 receptor antagonists
 - Bosentan: combined ETA and ETB receptor antagonist with modest short-term improvements in exercise tolerance, cardiac index,^{20,21} RV dilation²²; long-term efficacy uncertain
- Unproven therapy
 - Sildenafil: some short-term and case-report data to support clinical improvement²³⁻²⁵
 - Inhaled phosphodiesterase inhibitors
 - Nitric oxide
- Lung transplantation: the only cure for PPH⁴
- Pulmonary thrombectomy: improves functional status of patients with chronic, organized thrombi in large pulmonary arteries



Patient Care Warnings

- Do not initiate vasodilator therapy without supervision of a specialist; empiric therapy can lead to severe hypotension and death
- Safe and effective contraception is recommended for all women of childbearing age with severe pulmonary hypertension
- In SPH, the typical strategy is to treat the underlying disorder

References

- ③ 1. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med* 1997;336:111-17.
- ③ 2. Willerson J, Cohn J. Pulmonary hypertension. In: *Cardiovascular Medicine*, 2nd ed. Philadelphia, Churchill-Livingstone, 2000:1857-84.
- ③ 3. Palevsky HI, Fishman AP. Chronic cor pulmonale: Etiology and management. *J Am Med Assoc* 1990;263:2347-53.
- ③ 4. Runo JR, Loyd JE. Primary pulmonary hypertension. *Lancet* 2003;361:1533-44.
- ③ 5. Rich S. Pulmonary hypertension. In: Braunwald, E (ed.). *Heart Disease: A Textbook of Cardiovascular Medicine*, 6th ed. Philadelphia, WB Saunders, 2001:1908-35.
- ③ 6. Budev MM, Arroliga AC, Jennings CA, et al. Diagnosis and evaluation of pulmonary hypertension. *Clev Clin J Med* 2003;70:S9-S17.
- ③ 7. Fedullo PF, Auger WR, Kerr KM, et al. Chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2001;345:1465-72.
- ③ 8. Humbert M, Sitbon O, Simonneau G, et al. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004;351:1425-34.
- ③ 9. Gildea TR, Arroliga AC, Minai OA, et al. Treatments and strategies to optimize the comprehensive management of patients with pulmonary hypertension. *Clev Clin J Med* 2003;70:S18-S27.
- ② 10. Bjornsson J, Edwards WD. Primary pulmonary hypertension: A histopathological study of 80 cases. *Mayo Clin Proc* 1985;60:16-25.
- ③ 11. Sitbon O, Humbert M, Ioos V, et al. Who benefits from long-term calcium-channel blocker therapy in primary pulmonary hypertension? *Am J Respir Crit Care Med* 2003;157:A440.
- ① 12. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996;334:296-302.
- ② 13. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. *Circulation* 2002;106:1477-82.
- ② 14. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. *J Am Coll Cardiol* 2002;40:780-88.
- ① 15. Simonneau G, Barst RJ, Galiè N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with primary pulmonary arterial hypertension: A double-blind randomized controlled trial. *Am J Respir Crit Care Med* 2002;165:800-804.

16. Galiè N, Humbert M, Vachiéry JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: A randomized, double-blind placebo-controlled trial. *J Am Coll Cardiol* 2002;39:1496-1502.
17. Barst RJ, McGoon M, McLaughlin V, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;41:2119-25.
18. Hoeper MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000;342:1866-70.
19. Olschewski H, Simonneau G, Galiè N, et al. Inhaled iloprost in severe pulmonary hypertension. *N Engl J Med* 2002;347:322-27.
20. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.
21. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: A randomized placebo-controlled study. *Lancet* 2001;358:1119-23.
22. Galiè N, Hinderliter AL, Torbicki A, et al. Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and Doppler measures in patients with pulmonary arterial hypertension. *J Am Coll Cardiol* 2003;41:1380-86.
23. Wilkens H, Guth A, König J, et al. Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. *Circulation* 2001;104:1218-22.
24. Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: A randomized controlled trial. *Lancet* 2002;360:895-900.
25. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled nitric oxide for severe pulmonary hypertension. *Ann Intern Med* 2002;136:515-22.

APPROACH TO PULMONARY FUNCTION TESTS

Spirometry

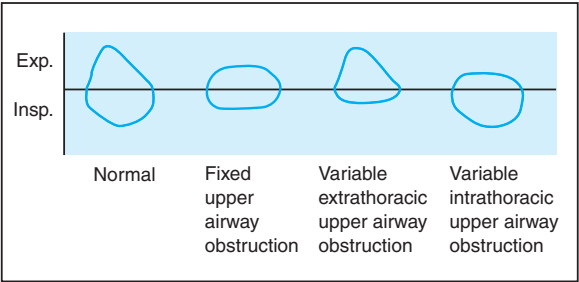
- Measures the volume of air exhaled or inhaled as a function of time
- Forced vital capacity (FVC): maximal exhalation effort from total lung capacity (TLC) to residual volume (RV)

- FEV_1 : forced expiratory volume in 1 second measured during FVC maneuver
- FEV_1/FVC ratio

SPIROMETRY PATTERNS		
	Obstruction	Restriction
FEV_1	↓	↓
FVC	↔ or ↑	↓
FEV_1/FVC	↓ (by definition)	↔ or ↑
RV	↑ if air trapping	↓
TLC	↑ if hyperexpansion	↓ (by definition)
DLCO	↓ (emphysema)	↔ or ↓
FEF 25%-75%	↓↓	↔

DLCO = diffusion capacity of the lung for carbon monoxide; FEF = forced expiratory flow
Adapted from reference 1

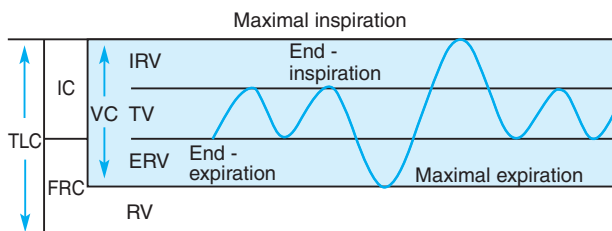
- Flow-volume loop: generated as a graphic display during spirometry
 - Adequacy
 - Rapid, smooth increase in flow to peak flow, then smooth decline in expiratory flow
 - Contour of loop must be free of artifact
 - Loop must be reproducible
 - Volume (or flow) versus time loops should reach 6 seconds or plateau



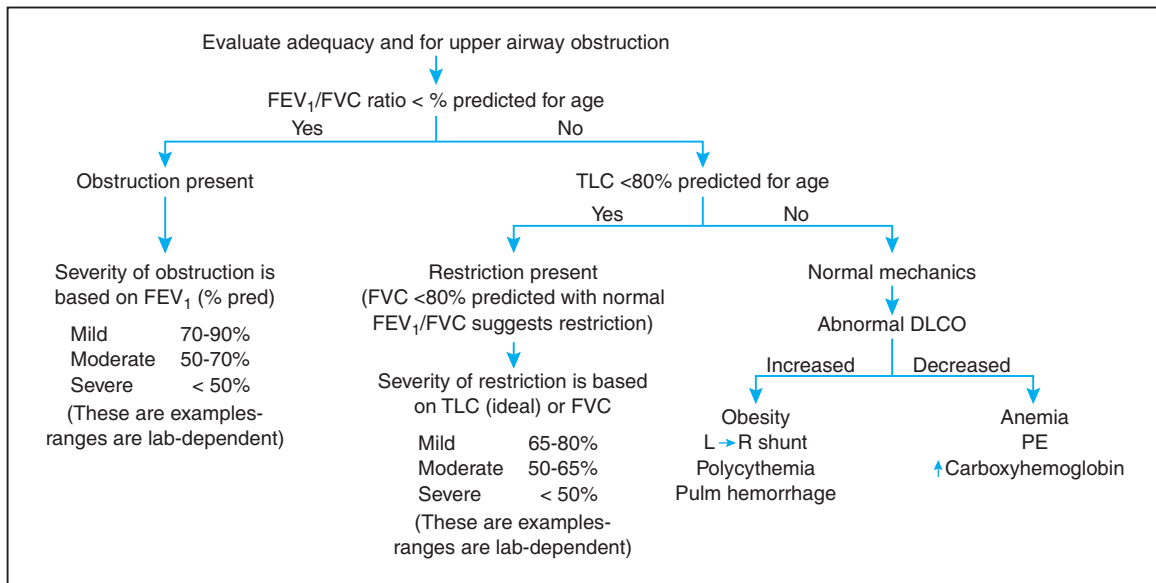
Large airway obstruction patterns. (Adapted from Hyatt RE, Scanlon PD. Interpretation of Pulmonary Function Tests. Philadelphia, Lippincott-Raven, 1997)

- Bronchodilator response (following two puffs of a β_2 agonist)
 - Positive response = increased FVC or FEV_1 by 12% and 200 mL from baseline
 - Defines asthma, predicts response to bronchodilator therapy, and has prognostic significance¹
- Bronchoprovocation²
 - Positive response: $\geq 20\%$ decrease in FEV_1 after inhalation of low-dose methacholine or histamine
 - Identifies patients with airway hyperreactivity (a hallmark of asthma)

Lung Volumes^{3,4}



- Determined using inert gas dilution, nitrogen washout, or body plethysmography; these techniques are not equivalent
- Total lung capacity (TLC)
 - Increased in obstructive processes if hyperexpansion or air-trapping is present
 - Reduced in restrictive processes (PAINT: Pleural, Alveolar, Interstitial, Neuromuscular, Thoracic cage)
- RV
 - Increased in obstructive processes due to expiratory airway collapse and air-trapping
 - Reduced in restrictive processes
 - Effort dependent on plethysmography



Approach to PFT Interpretation. (Adapted from Becklake M, Crapo RO. American Thoracic Society. Lung function testing: Selection of reference values and interpretive strategies. Am Rev Respir Dis 1991;144:1202-18.).

Diffusion Capacity (DLCO)⁴

- Measures the number of functioning alveolar-capillary units involved in gas exchange
- Can be adjusted for hemoglobin level
- Obstruction: DLCO decreases with larger degrees of emphysema but typically is normal in diseases limited to the conducting airways (asthma, bronchitis, bronchiolitis) due to increased intrathoracic blood volume
- Interstitial disease is associated with a low DLCO that may normalize when correcting for the low inspired gas volume (D_L/VA); a low DLCO due to extrinsic causes (e.g., obesity, kyphoscoliosis) always corrects
 - The first abnormality in interstitial lung diseases on static pulmonary function test is a reduced DLCO
- Other causes of abnormal DLCO
 - Increased DLCO: pulmonary hemorrhage, obesity (after correction for volume), left-to-right cardiac shunt, polycythemia
 - Decreased DLCO: anemia, pulmonary vascular disease (e.g., pulmonary edema), elevated carboxyhemoglobin levels (recent smoking), interstitial lung disease, emphysema, or any disturbance at the alveolar-capillary interface

References

- ③ 1. Hyatt RE, Scanlon PD. Interpretation of Pulmonary Function Tests. Philadelphia, Lippincott-Raven, 1997.
- ③ 2. American Thoracic Society. Guidelines for methacholine and exercise challenge testing. *Am J Respir Crit Care Med* 2000;161:309-29.
- ③ 3. Ruppel G. AARC practice guidelines. Static lung volumes: 2001 revision and update. *Respir Care* 2001;46:531-39.
- ③ 4. Hughes JMB, Pride NB. Lung Function Tests. Philadelphia, WB Saunders, 1999.
- ③ 5. Becklake M, Crapo RO. American Thoracic Society. Lung function testing: Selection of reference values and interpretive strategies. *Am Rev Respir Dis* 1991;144:1202-18.

INDICATIONS FOR EMERGENT BRONCHOSCOPY

Description of Terms

- Bronchoscopy enables direct visual examination of the upper airways and tracheobronchial tree, sampling of respiratory tract secretions for culture and cytology, and direct tissue biopsy¹
- Flexible bronchoscopy: used for most diagnostic procedures
- Rigid bronchoscopy: used for certain therapeutic procedures (e.g., stenting, laser therapy), foreign body extraction, and for patients with massive hemoptysis

Acute Indications

- Massive hemoptysis (>200 cc/d): localize source of bleeding, determine need for other therapies (e.g., steroids), or to stop hemorrhage (through tamponade or medications) when lung resection and interventional radiological embolization are not appropriate; rigid bronchoscopy is preferred
- Retained secretions and atelectasis: when suctioning, bronchodilators, and chest percussion therapy fail
- Endobronchial obstruction/airway strictures: rigid bronchoscopy often used for laser therapy and stenting^{2,3}
- Facilitates difficult placement of endotracheal tube
- Removal of foreign body: rigid bronchoscopy preferred
- Smoke inhalation injury/noxious fumes: identification of early inflammation or laryngeal edema; can help determine the need for intubation

- Traumatic airway injury: evaluates tears or disruption in trachea and/or mainstem bronchi

Contraindications to Bronchoscopy⁴

Absolute Contraindications

- Lack of consent or trained personnel
- Inadequate equipment and facilities

Relative Contraindications

- Recent myocardial infarction (within 6 weeks) or unstable angina
- Uncontrolled arrhythmias
- Tracheal obstruction
- Unstable asthma
- Refractory hypoxemia/hypercarbia
- Uremia
- Pulmonary hypertension
- Thrombocytopenia, coagulopathy
- Uncooperative patient
- Positive pressure ventilation with positive end-expiratory pressure

Additional Rigid Bronchoscopy Contraindications

- Unstable neck, rheumatoid arthritis
- Cervical spine immobility
- Restricted temporomandibular joint mobility



Patient Care Warnings

- Bronchoscopy should be performed only by experienced staff
- Involve consultants early if emergent bronchoscopy is warranted

References

- ③ 1. Raoof S, Mehrishi S, Prakash U. Role of bronchoscopy in modern medical intensive care unit. *Clin Chest Med* 2001; 22:241-61.
- ③ 2. Colt HG, Harrell JH. Therapeutic rigid bronchoscopy allows level of care changes in patients with acute respiratory failure from central airways obstruction. *Chest* 1997;112:202-206.
- ③ 3. Mehta AC, DasGupta A. Airway stents. *Clin Chest Med* 1999;20:139-51.
- ③ 4. Sokolowski JW Jr, Burgher LW, Jones FL Jr, et al. Guidelines for fiberoptic bronchoscopy in adults. Position paper of the American Thoracic Society Board of Directors. *Am Rev Respir Dis* 1987;136:1066.

DIFFERENTIAL DIAGNOSES IN THORACIC RADIOLOGY

Thoracic Imaging Modalities

- Chest x-ray
 - Posteroanterior and lateral images are cornerstones of all thoracic imaging
 - Compare all new films with older films if available
- Computed tomography (CT) scan: includes high-resolution and CT angiography
- Others: magnetic resonance imaging (MRI), ventilation/perfusion scanning (V/Q scan), ultrasound (for localizing effusions), positron emission tomography (PET)

Types of Parenchymal Disease

Alveolar Filling Pattern/Opacification

- Focal airspace disease
 - Lobar pneumonia
 - Lung abscess
 - Lobar collapse
 - Malignancy (primary lung or single metastatic lesion)

- Pulmonary hemorrhage or infarction
- Iatrogenic (radiation, drug toxicity)
- Chronic opacification: also consider bronchiolitis obliterans with organizing pneumonia (BOOP); tuberculosis (TB); fungal, eosinophilic pneumonia
- Diffuse airspace disease:
 - Pulmonary edema (cardiogenic vs. noncardiogenic)
 - Pneumonia
 - Hemorrhage
 - Acute respiratory distress syndrome (ARDS)
 - Aspiration
 - Chronic: also consider malignancy, BOOP, vasculitis, eosinophilic pneumonia, alveolar proteinosis
- Unilateral opacification:
 - Large effusion (including hemothorax)
 - Pulmonary collapse
 - Pneumonia
 - Pneumonectomy
 - Tumor (either intra- or extrathoracic)
 - Pulmonary agenesis
 - Radiation pneumonitis

Interstitial Process

- Acute:
 - Pulmonary edema
 - Pneumonia
 - Hypersensitivity pneumonitis (HP)
- Chronic:
 - Chronic pulmonary edema
 - Infection (e.g., *Pneumocystis carinii* pneumonia [PCP], mycoplasma)
 - Fibrosis (see below)
 - Lymphangitic carcinomatosis
 - Lymphocytic interstitial pneumonia (LIP)
 - Allergic alveolitis
 - Sarcoidosis

- Fibrosis:
 - Cryptogenic
 - Occupational (asbestosis, allergic alveolitis)
 - Infection (TB, psittacosis, aspiration pneumonia)
 - Collagen vascular disease (scleroderma, systemic lupus erythematosus [SLE], rheumatoid arthritis [RA])
 - Sarcoidosis
 - Iatrogenic (amiodarone, busulfan, radiotherapy)
- Interstitial disease with:
 - Pleural effusion: congestive heart failure (CHF), SLE, RA, pneumonia, lymphangitic carcinomatosis
 - Adenopathy: sarcoidosis, lymphoma/leukemia, fungal or TB, silicosis
 - Migration: pulmonary edema, eosinophilic pneumonia
- Diffuse reticulonodular pattern:
 - Idiopathic fibrosis (fibrosing alveolitis, usual interstitial pneumonia, desquamative interstitial pneumonia, idiopathic pulmonary fibrosis)
 - Drug-related
 - Connective tissue diseases (RA, SLE, dermatomyositis, Sjögren's syndrome)
 - Granulomatous disease (histoplasmosis, TB, etc.)
 - ARDS
 - Silicosis
 - Asbestosis
 - Chronic aspiration (predominantly lower lobes)
 - Lymphangitic carcinomatosis
 - Lymphoma
 - Sjögren's syndrome

Location of Disease

Upper Lung

- Pneumonia
- Reactivation tuberculosis
- Cystic fibrosis

- Silicosis
- Sarcoidosis
- Eosinophilic granuloma

Lower Lung

- Aspiration pneumonia
- Lipoid pneumonia
- Pulmonary fibrosis (idiopathic, collagen vascular disease, asbestosis, drugs)
- Metastases
- Bronchiectasis (most commonly)

Perihilar

- Pulmonary edema (batwing appearance with peripheral sparing)
- PCP
- Inhalation injury
- Vasculitis or pulmonary hemorrhage
- Aspiration pneumonia
- Sarcoidosis
- Bronchitis or bronchiectasis
- Viral pneumonia

Peripheral

- Pulmonary fibrosis (idiopathic, scleroderma, rheumatoid, asbestosis)
- Metastatic disease
- Sarcoidosis
- Eosinophilic pneumonia
- BOOP
- Hypersensitivity pneumonitis

Nodules and Masses

Solitary Pulmonary Nodule (<3 cm)

- Granuloma (tuberculoma or histoplasmosis)
- Infectious (septic embolus, abscess, fungus)

- Neoplasm (bronchogenic carcinoma, solitary metastasis, hamartoma, bronchial carcinoid)
- Vascular (prominent vessel on end, arteriovenous malformation, hematoma)
- Bronchogenic cyst
- Mimics
 - Extracorporeal: “buttons,” “jewelry,” etc.
 - Cutaneous: nipple shadow, nevi, neurofibroma, keloid, breast fibroadenoma
 - Chest wall: bone islands, healed fractures, large costochondral junction
 - Pleural: fibrous tumors, lipoma

Lung Mass (>3 cm)

- Neoplasm (bronchogenic carcinoma, hamartoma, metastasis)
- Round pneumonia
- Abscess
- Fungus (cryptococcosis, blastomycosis, coccidioidomycosis, histoplasmosis)
- Rounded atelectasis
- Hematoma
- Wegener’s granulomatosis
- Pseudotumor

Multiple Pulmonary Nodules

- Pulmonary metastasis (breast, kidney, colon, head and neck, testicular, thyroid, melanoma)
- Invasive aspergillosis
- Wegener’s granulomatosis
- Rheumatoid nodules
- Nodular sarcoidosis
- Septic emboli
- Kaposi’s sarcoma
- Nodular amyloidosis
- Pulmonary AVMs
- Multiple parenchymal hematomas

Numerous Calcified Nodules

- Healed granulomatous disease (TB, histoplasmosis, coccidioidomycosis)
- Varicella (usually lower lobe)
- Silicosis (usually upper lobe)
- Metastatic calcification in chronic kidney disease
- Lymphoma after radiotherapy
- Chronic pulmonary venous hypertension in mitral stenosis

Miliary Patterns

- Miliary tuberculosis (3-5 mm)
- Histoplasmosis
- Varicella (<5 mm)
- Silicosis (1-10 mm)
- Kaposi's sarcoma

Cystic and Cavitary Lesions

Cystic Lung Lesions (Wall Thickness ≤ 4 mm)

- Bulla (diameter >1 cm) or bleb (diameter <1 cm)
- Pneumatocele
- Congenital cystic lesions (e.g., bronchogenic cyst)
- Infection (coccidioidomycosis, PCP, *Echinococcus*)
- Traumatic cysts

Cavitary Lesions (Wall Thickness > 4 mm or Surrounding Infiltrate/Mass)

- Neoplasm (bronchogenic carcinoma, metastasis, lymphomas)
- Infection or abscess (bacterial, mycobacterial, fungal, parasitic)
- Septic embolism
- Immunological (Wegener's granulomatosis, rheumatoid nodule)
- Focal bronchiectasis
- Pulmonary infarction
- Progressive massive fibrosis in pneumoconioses

- Congenital lesion (sequestration, adenomatoid malformation)

Diffuse Cystic or Cavitary Lesions

- Lymphangiomyelomatosis
- Pulmonary Langerhans' cell histiocytosis
- Honeycombing (interstitial lung disease, asbestosis, hypersensitivity pneumonitis)
- Advanced sarcoidosis
- Diffuse bronchiectasis
- Metastatic disease

Multiple Cavitary Nodules

- Septic emboli
- Fungal infections (coccidioidomycosis, *Aspergillus*)
- Metastases (squamous cell, sarcomas)
- Eosinophilic granulomas
- Wegener's granulomatosis
- Silicosis

Hyperlucent Lung

- Normal lung (rotated, contralateral pleural effusion in supine view)
- Pneumothorax and tension pneumothorax
- Emphysema (hyperinflation, oligemia, bulla, blebs)
- Pulmonary embolism (Westermark's sign)
- Mastectomy, Poland's syndrome
- Endobronchial mass
- Foreign body aspiration
- Swyer-James syndrome (children)

Mediastinal Processes

- Superior (thoracic inlet): area above line between the sternal angle and fourth disk space
 - Thyroid goiter or mass
 - Lymphoma

- Adenopathy
- Tortuous brachiocephalic vessels
- Thymic mass
- Anterior: bounded anteriorly by sternum and posteriorly by the anterior pericardium
 - Thymic mass
 - Thyroid goiter or mass
 - Teratoma or other germ cell neoplasm
 - Lymphoma or other adenomatous process (e.g., Castleman's disease)
 - Mediastinal lipomatosis
- Middle: contains heart, roots of great vessels, pericardium, trachea, and bronchi
 - Vascular: ascending aortic aneurysm, enlarged azygos vein, tortuous brachiocephalic vessels
 - Lymphadenopathy (lymphoma, bronchogenic carcinoma, sarcoidosis, reactive adenopathy, metastatic disease)
 - Mediastinitis (esophageal perforation, rupture, or infection)
 - Primary tumor: bronchogenic (small cell), tracheal, parathyroid
 - Bronchogenic or esophageal cyst
- Posterior: between posterior pericardium and paravertebral gutters
 - Neurogenic tumor
 - Paraspinal abscess
 - Hiatal hernia
 - Esophageal abnormalities: achalasia, tumors
 - Descending thoracic aneurysm
 - Pulmonary or pleural mimics (loculated effusion, lipoma, rounded atelectasis)

Hilar Enlargement

- Bilateral
- Sarcoidosis
- Neoplasm: lymphoma, bronchial carcinoma, metastatic tumors

- Infections: tuberculosis, AIDS, recurrent chest infections
- Castleman's disease
- Silicosis
- Berylliosis
- Phenytoin therapy
- Vascular: pulmonary artery hypertension
- Asymmetric
- Neoplasm: small cell or squamous cell, primary mediastinal tumor, metastatic disease
- Granulomatous disease (TB, coccidioidomycosis, histoplasmosis)
- Unilateral pneumonia or lung abscess
- Pulmonary artery enlargement
- Sarcoidosis (rarely unilateral)
- Calcified hilar lymphadenopathy
- Prior granulomatous infection (TB, fungal)
- Silicosis (associated with upper lung nodules)
- Treated lymphoma (eggshell pattern)

Tracheal Abnormalities

- Enlargement
- Tracheomalacia
- Tracheobronchomegaly (Mounier-Kuhn syndrome)
- Cystic fibrosis
- Relapsing polychondritis
- Postradiation
- Stenosis
- Post-traumatic or postintubation
- TB
- Fungal infections
- Wegener's granulomatosis

Pleural Densities

- Effusion
- Extrapleural fat
- Asbestos plaques or thickening

- Mesothelioma
- Localized fibrous tumor
- Pleural sarcoma
- Pseudotumor

Diaphragmatic Abnormalities

- Morgagni's hernia (usually right-sided between sternal and costal diaphragm)
- Bochdalek's hernia (90% left-sided posterolateral congenital defect)
- Diaphragmatic eventration
- Traumatic rupture

Enlarged Heart

- CHF, dilated cardiomyopathy
- Pericardial effusion
- Valvular heart disease (enlarged left atrium in mitral stenosis)
- Atrial or ventricular aneurysm

Differential Diagnosis of Pneumonias

- Lobar pneumonia: intra-alveolar spread of exudates, cordoned by fissures between lobes (*Streptococcus*, *Legionella*, *Haemophilus*, *Klebsiella*, *Staphylococcus aureus*, *Pseudomonas*)
- Bronchopneumonia: patchy infiltrates along the conducting airways (*S. aureus*, *Pseudomonas*, anaerobes)
- Interstitial: reticular appearance, extending along septal margins of lung (viral and atypical pneumonias)
- Diffuse pneumonia: can be caused by most pathogenic pulmonary infections

- AIDS and similar immunosuppressed patients (*Pneumocystis pneumonia*, bacterial, fungal)
- Viral (influenza, adenoviral)
- Nosocomial (gram-negative bacteria)
- Mycobacterial
 - Primary TB affects children and elderly: affects mid-lower lobes with hilar adenopathy
 - Reactivation TB: apical-posterior cavitory lung lesion; endobronchial occlusion can occur from granuloma or eroding lymph node; postinflammatory bronchiectasis often observed in right middle lobe; mycetoma may occur in tuberculous cavities
 - CT scans can show “tree-in-bud” pattern, suggestive of active endobronchial disease (but also occurs in other bronchiolar infections)

Pulmonary Metastases

- Cancers most likely to metastasize to the lungs are choriocarcinoma, melanoma, sarcoma, renal cell carcinoma, thyroid cancer, breast cancer, and testicular cancer
- Most likely origin of metastases based on incidence: breast > renal cell > head and neck > colon cancer
- Large lesions (cannonball)
 - Sarcoma
 - Testicular
 - Renal cell
 - Thyroid cancer
 - Colon cancer
- Small lesions
 - Melanoma
 - Thyroid cancer
 - Breast cancer
 - Renal cell carcinoma

- Calcified lesions
 - Osteosarcoma
 - Chondrosarcoma
 - Mucinous adenocarcinoma

Pneumothorax

- Trauma
- Iatrogenic
- Volutrauma from positive pressure ventilation
- Ruptured cystic airspace (see above)
- Barotrauma (e.g., scuba diving)
- Necrotizing pneumonia or ruptured abscess
- Bronchopleural fistula
- Pulmonary fibrosis
- Esophageal rupture
- Pulmonary metastases
- Bronchogenic carcinoma
- Catamenial (endometrial implants)

CRITICAL CARE TOXIDROMES

Lithium Toxicity

Definition, Etiology, and Epidemiology

- Incidence in 2002: 4954 cases (1630 unintentional), 280 major toxicities, 16 deaths¹
- Occurs in three settings²
 - Acute overdose in lithium-naïve patients
 - Acute on chronic: overdose in patient on chronic lithium therapy
 - Chronic toxicity: usually from dosage change or decreased renal function
- Most commonly due to acute ingestions³
- Pharmacology
 - Gastrointestinal (GI) absorption is rapid and complete at 8 hours after oral administration: with peak plasma levels at 2–5 hours but may be up to 3–4 days with sustained release preparations, which are more commonly available^{2,4}
 - Very narrow toxic-to-therapeutic ratio
 - Volume of distribution (Vd) approximates total body water (Vd 0.7–0.9 L/kg)^{2,4}
 - Distribution to brain delayed approximately 24 hours² with no protein or tissue binding
 - Almost completely excreted by the kidneys (~5% in sweat); freely filtered, with 80% reabsorbed (following sodium)²
 - Serum half-life is 12–27 hours following single dose; half-life increases in the elderly and with chronic use^{2,4}

Pearls of the History and Physical Examination

- Risk factors for decreased lithium excretion secondary to impaired renal function
 - Older age
 - Volume depletion (infection, gastroenteritis, surgery; diuretic use: especially thiazides)⁴
 - Decreased effective arterial volume (congestive heart failure, cirrhosis, nephrosis)⁴
 - Drugs: especially nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors, others (cyclosporine, tetracycline)^{2,4}
- Acute symptoms:
 - Mild toxicity: lethargy, drowsiness, fine tremor, muscle weakness, nausea, vomiting, and diarrhea²
 - Moderate toxicity: coarse tremor, confusion, dysarthria, nystagmus, ataxia, myoclonic twitches, and electrocardiogram changes (ST depression and inverted T waves over precordium)²
 - Severe toxicity: grossly impaired consciousness, increased deep tendon reflexes, seizures, syncope, renal insufficiency, death²
- Altered mental status is the most common manifestation
- Peripheral neuropathy and myopathy are rare manifestations
- Acute symptoms often in setting of chronic complications of use: nephrogenic diabetes insipidus (polyuria, polydipsia), leukocytosis, goiter (usually without clinical thyroid disease)³
- Increased risk of neuroleptic malignant syndrome (NMS) with concurrent neuroleptic use

Diagnostic Studies and Laboratory Values

- Lithium plasma concentrations
 - In acute ingestions, level may not correlate with clinical status because of insufficient time for equilibration between serum and CNS⁵
 - Better correlation between plasma levels and

symptoms with chronic therapy,⁵ but toxic symptoms may occasionally be present with lithium levels within the therapeutic range²

- Usually 1.5–2.0 mEq/L with mild toxicity²⁻⁴
- Usually 2.0–2.5 mEq/L with moderate toxicity²⁻⁴
- Usually above 2.5 mEq/L with severe toxicity²⁻⁴
- Life-threatening >3.5 mEq/L or 4 mEq/L, depending on source³
- Leukocytosis: both acute and chronic; rarely leukopenia²
- Modest reduction in anion gap: usually with Li levels >3.5 mEq/L
- Check thyroid function to monitor for hyper- or hypothyroidism²
- Kidney, ureter, and bladder study to assess for metallic pills in gastrointestinal tract

Guide to Acute Management

Supportive Care

- Protection of airway if level of consciousness is decreased
- Stopping other drugs that may have additive side effects (phenothiazines or haloperidol)
- Consider intensive care unit admission for severe intoxication or for patients with moderate toxicity and significant comorbid conditions³
- Most patients completely resolve the complications of toxicity, but long-term or permanent neurological sequelae (usually cerebellar dysfunction) have been documented^{3,4} in up to 10% of cases with lithium levels greater than 6 mEq/L
- Death is usually due to complications of prolonged coma or respiratory failure³

GI Decontamination

- Ipecac can be considered in early presentation (<1 hour after ingestion)

- Charcoal does not limit absorption of Li^+ (but consider for other potential concurrent drug ingestions)³
- Gastric lavage is indicated as initial treatment of significant acute ingestion of lithium^{3,4}
- Whole bowel irrigation with polyethylene glycol may be effective for acute ingestion of sustained-release formulations; efficacy data limited to case reports^{4,6}

Enhancing Excretion

- Correct volume depletion with isotonic intravenous fluid (IVF), preferably crystalloid²⁻⁴
 - Follow Na closely as IVF can cause hyponatremia without also correcting ongoing free water losses in urine
- IVF with a forced diuresis not recommended as it usually does not enhance excretion consistently and increases risk of hyponatremia in patients who are normovolemic²⁻⁴

Hemodialysis (HD)

- Li is one of the most dialyzable toxins²; slow equilibrium between extra- and intracellular lithium can lead to rebound increase in plasma levels after stopping dialysis (can also get rebound from sustained-release preparation and continued GI absorption)²
- Indications for HD^{2,6}
 - Any patient with lithium intoxication who presents with coma, convulsions, respiratory failure, deteriorating mental status, or renal failure (neurological symptoms are the most important indication for HD)
 - Lithium level >6 mEq/L in any patient or >4 mEq/L in patients on chronic therapy (regardless of presence of symptoms)
 - Symptomatic patients with levels of >4.5 mEq/L who are lithium-naïve; >2.5 mEq/L in patients on chronic therapy

- Lithium level 2.5–4 in any patient with severe neurological symptoms, renal insufficiency, or hemodynamically or neurologically unstable
- Lithium level <2.5 mEq/L in patients with end-stage renal disease (ESRD), or whose lithium level increases after admission, or who fails to reach lithium level below 1 mEq/L within 30 hours
- Continue to check lithium levels frequently, even after hemodialysis, because of rebound increase: may necessitate further hemodialysis²
- Continuous arteriovenous hemodiafiltration and HD followed by continuous veno-venous hemofiltration have been investigated as a means of preventing rebound in severe lithium toxicity and may be particularly useful with chronic poisoning; not yet standard therapy²



Patient Care Warnings

- Toxic lithium symptoms may occasionally occur with “therapeutic” lithium levels in patients who take the medication chronically
- Monitor closely for post-hemodialysis rebound in lithium levels

References

- ③ 1. American Association of Poison Control Centers. Web site annual report 2002: www.aapcc.org
- ③ 2. Timmer TT, Sands JM. Lithium intoxication. *J Am Soc Nephrol* 1999;10:666-74.
- ③ 3. Groleau, G. Lithium toxicity: Concepts and controversies in toxicology. *Emerg Med Clin North Am* 1994;12:511-31.
- ③ 4. Okusa ND, Crystal LJ. Clinical manifestations and management of acute lithium intoxication. *Am J Med* 1994;97:383-89.
- ③ 5. Dawson AH, Whyte IM. Therapeutic drug monitoring in drug overdose. *Br J Clin Pharmacol* 2001;52: 97S-102S.
- ③ 6. Borkan, SC. Extracorporeal therapies for acute intoxications. *Crit Care Clin* 2002;18:393-420.

Acetaminophen Toxicity

Definition, Etiology, and Epidemiology

- In 2002: 51,377 exposures, 902 major toxicities, 119 deaths¹
- Pharmacodynamics of acetaminophen (APAP)
 - All formulations are readily absorbed, with peak plasma concentrations achieved 30 minutes to 2 hours after a therapeutic dose (10–15 mg/kg)²
 - Elimination kinetics are first order, with 2–4 hour half-life (longer in infants and young children, the elderly, and patients with hepatic dysfunction)²
 - Predominately hepatically metabolized²
 - 90% metabolized to inactive glucuronide and sulfate conjugates
 - 5% excreted unchanged in urine
 - 5% metabolized by P450 mixed oxidase system to N-acetyl-para-benzoquinoneimine (NAPQI); NAPQI is reduced by the sulfhydryl group of glutathione to form a nontoxic mercapturate conjugate
 - If glutathione stores fall to less than 30% of normal: toxicity due to NAPQI occurs
- Risk of toxicity occurs after acute ingestions, with 140–150 mg/kg in children or approximately 7.5 g in adults²
- No validated guidelines to estimate toxic doses after multiple ingestions or chronic ingestions²; manufacturer guidelines advise against doses >4 g/d

Pearls of the History and Physical Examination

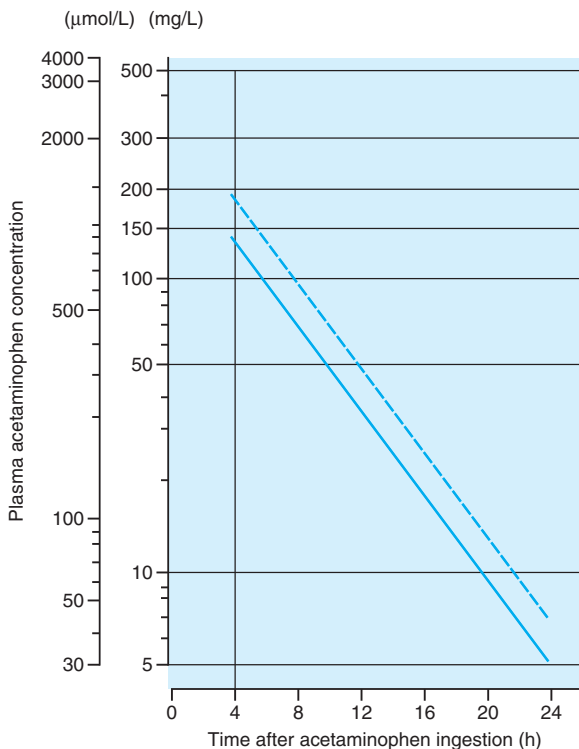
- Information regarding amount of ingestion if available and reliable (witnessed by a reliable observer): less than 150 mg/kg in children and 7.5 g in adults for one-time acute ingestions do not need further evaluation for APAP toxicity² except when >4 hours from ingestion

- Many products contain APAP, and patients may not realize they have been unknowingly ingesting to toxic levels
- Manifestations of liver injury may not be seen on initial presentation, and presenting complaints may be nonspecific; patients can be completely asymptomatic
- Symptoms often progress from diaphoresis to nausea/vomiting to jaundice/abdominal discomfort/right upper quadrant pain to encephalopathy/coma²
- Fatalities usually occur between days 3–5 but have been reported at other times: usually from multiorgan system failure or single overwhelming complication from hepatic failure (e.g. hemorrhage, acute respiratory distress syndrome, cerebral edema)²

Diagnostic Studies and Laboratory Values

- APAP level
 - Therapeutic: 10–20 $\mu\text{g/mL}$
 - Check APAP level in all cases of poisoning; should be done routinely in any case where the history is likely to be unreliable (e.g., altered mental status, active suicidal intent)
 - Rumack-Matthew nomogram: works only for single acute ingestion
 - Measure repeat level of APAP after 4 hours²
 - Upper line is the original hepatotoxicity risk line: still used in Europe and Canada²
 - Lower line is used in most places in the United States: is 25% below the original line to prevent diagnostic errors caused by inaccuracies in laboratory assessment, history, and other individual variations²
 - Values even slightly below the lower line can be regarded as nontoxic²
- Elevated hepatic enzymes (aspartate transaminase [AST] is the most sensitive and earliest to rise), bilirubin, prothrombin time (PT), hypoglycemia, metabolic acidosis

- Renal function abnormalities occur in as many as 25% of patients with documented hepatotoxicity²



The Rumack-Matthew Nomogram for Predicting Acetaminophen Hepatotoxicity. Treatment lines for acetaminophen hepatotoxicity. The upper (broken) line is the line suggested by Rumack and Matthew, also known as the "probable hepatotoxicity line." The lower (solid) line is the "possible hepatotoxicity line," arbitrarily drawn 25% lower in order to allow for possible laboratory errors and inaccuracy in history-taking. (Adapted from Smilkstein MJ, et al. Efficacy of N-acetylcysteine in the treatment of acetaminophen overdose: Analysis of the multicenter study [1976-1985]. *N Engl J Med* 1988; 319:1557-62; and Mokhlesi B, et al. *Chest* 2003;123:897-922.)

Guide to Acute Management

- Monitor closely for hypoglycemia, electrolyte disturbances, and evidence of cerebral edema

Gastrointestinal Decontamination

- Gastric emptying: useful only within 1–2 hours or for possible coingestants²
- Activated charcoal: concern for use of activated charcoal (AC) and N-acetylcysteine (NAC) together as AC may decrease absorption of oral NAC; when possible, it is reasonable to space out the doses of AC and NAC by 1–2 hours; however, when this is not possible, both can be given together without dose adjustment of either drug²
 - Single dose of AC should be given if less than 4 hours from ingestion
 - Over 4 hours from ingestion: no reason to give AC (unless needed for coingestants)²

N-Acetylcysteine

- Treatment of choice for APAP overdose; enhances glutathione supply, therefore increasing ability to reduce NAPQI to nontoxic forms²
- Oral NAC
 - 140 mg/kg loading dose, then 70 mg/kg every 4 hours for 17 additional doses (1330 mg/kg over 68 hours)²
 - Of patients who were in “probable risk” area of nomogram, none died if therapy administered within 24 hours, but there was an increasing risk of severe liver damage with delay of treatment greater 10 hours³
- IV NAC (Acetadote): approved for use in United States in 2004
 - 20-hour regimen: 150 mg/kg bolus over 15 minutes, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours (300 mg/kg over 20 hours)⁴
 - Nonrandomized study of 100 patients: no deaths out of 62 patients when treatment started within 10 hours, only one with severe liver damage (1.6%); of

38 patients with treatment started after 10 hours:²

deaths (5%) and 20 (53%) with severe liver damage⁴

- 48-hour regimen not used in United States
- None of above regimens have been shown to be superior: each is very effective when initiated within 10 hours of ingestions⁴⁻⁷
- Late NAC therapy
 - Standard of care in United States has been to administer as late as 24 hours after ingestion^{2,8}; benefits decrease after 15–16 hours, with greatest benefit being within 10 hours
 - Late NAC not studied in patients without fulminant hepatic failure; use of late NAC is speculative in these patients²
 - Some authors recommend NAC treatment for any patient with plasma APAP concentration above the level of detection (more than 24 hours from acute overdose) or an abnormal aspartate aminotransferase (AST)
 - Start NAC; if APAP concentration falls to undetectable and no elevation in AST by 36 hours postingestion, then stop NAC²
 - If AST become elevated by 36 hours: hepatotoxicity is present and full course of NAC is warranted²

Chronic or Repeated APAP Ingestions

- Nomogram has no validity
- Repeated dosing shown to be a serious concern only in young children with acute febrile illness, alcoholics, and patients with chronic anticonvulsant use²
- Supratherapeutic ingestion histories (e.g., more than 10 g/day) or symptoms consistent with toxicity need prompt evaluation for APAP toxicity in patients not included in the groups mentioned above²
- High-risk groups: recommend evaluation for symptomatic patients or with history suggesting greater

than 10 mg/kg in children or 7.5 g in adults within a single 24-hour period

- Chronic APAP ingestions should be managed as above for late NAC, with monitoring of APAP level and AST over 36 hours

Special Cases

- Users of alcohol and other inducers of cytochrome p450 mixed-function oxidase system are at increased risk of APAP toxicity, but there are no data to support any change in management of acute ingestions
- Pregnancy: IV NAC is generally recommended due to concerns regarding sufficient placental transfer; NAC is safe for the fetus
- Pediatrics: children may be at lower risk for hepatotoxicity, but is still the general consensus that they be treated by the same guidelines as for adults²
- Hepatic failure: studies have shown benefit of IV NAC given late to patients already in fulminant hepatic failure (defined as AST >1000) from APAP toxicity who had not previously received NAC^{2,6}



Patient Care Warnings

- Efficacy of NAC decreases if therapy started after 10 hours, so it is extremely important to begin NAC therapy within this period if possible
- Early referral to toxicologist and/or poison control center for aid in management

References

- ③ 1. American Association of Poison Control Centers. Web site annual report 2002: www.aapcc.org.
- ③ 2. Anker AL, Smilkstein MJ. Acetaminophen concepts and controversies. *Emerg Med Clin North Am* 1994;12:335–49.
- ③ 3. Rumack, BH, et al. Acetaminophen overdose: 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med* 1981;141:380–85.
- ③ 4. Prescott LF, et al. Intravenous N-acetylcysteine: The treatment of choice for paracetamol poisoning. *Br Med J* 1979;2:1097–1100.
- ② 5. Yip L, Dart R, Hurlbut K. Intravenous administration of oral N-acetylcysteine. *Crit Care Med* 1998;26:40–43.
- ② 6. Keays R, et al. Intravenous acetylcysteine in paracetamol-induced fulminant hepatic failure: A prospective controlled trial. *Br Med J* 1991;303:1026–29.
- ③ 7. Smilkstein MJ, et al. Acetaminophen overdose: A 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med* 1991;10:1058–63.
- ② 8. Harrison PM, et al. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990;335:1572–73.

Aspirin Toxicity

Definition, Etiology, and Epidemiology

- 17,201 cases, 330 major toxicities, 62 deaths in 2002¹
- >100 mg/kg represents potentially serious ingestion²
- Caution for other substances that contain salicylates (oil of wintergreen [methyl salicylate], Pepto-Bismol)

Pearls of the History and Physical Examination

- Tinnitus may occur within the therapeutic range (20 mg/dL) but usually ~30 mg/dL
- Early symptoms of acute ingestion: nausea, vomiting, tinnitus, sweating, vertigo, fever, diarrhea, and hyperventilation when serum level above 20–30 mg/dL³
- Late/severe symptoms: altered mental status, coma,

noncardiogenic pulmonary edema, cerebral edema, acute lung injury, adult respiratory distress syndrome (ARDS), death

- Chronic intoxication: hyperventilation, tremor, papilledema, agitation, paranoia, bizarre behavior, memory deficits, confusion, and stupor; neurological abnormalities are much more common in chronic ingestions³
- Consider acetylsalicylic acid (ASA) toxicity in all patients with unexplained altered mental status (AMS), unexplained noncardiogenic pulmonary edema, and mixed acid-base disturbances³

Diagnostic Studies and Laboratory Values

- Salicylate level
 - Usual therapeutic range: 20–35 mg/dL⁴; *Warning*: some laboratories use mg/L
 - Signs of intoxication generally occur at level of 40–50 mg/dL⁴
 - Consider ICU monitoring with levels >65 mg/dL²
- Acid-base disturbances: classically have anion gap acidosis with respiratory alkalosis (usually with alkalemia) occurring in approximately 50% of patients with pure ingestion; non-gap metabolic acidosis and respiratory acidosis are both more common with coingestants and in pediatric population⁴
 - Anion gap is due to accumulation of lactate and ketoacids and, to a much lesser extent, salicylate itself⁴
- Hypouricemia^{3,4}
- Laboratory findings: increased prothrombin time (PT), platelet dysfunction, and proteinuria (acute overdose); increased liver function tests (LFTs), increased PT (secondary to hypoprothrombinemia), platelet dysfunction, and renal failure more commonly seen with chronic ingestion
- Chest x-ray: evaluate for noncardiogenic pulmonary edema

Guide to Acute Management

Supportive Care

- Supplemental glucose in all patients with AMS or with hypoglycemia; aspirin intoxication can lower central nervous system (CNS) glucose levels even with normal serum glucose levels³
- Volume expansion as most patients are volume-depleted (volume depletion will hinder attempts at urinary alkalinization later); monitor closely for non-cardiogenic pulmonary edema or adult respiratory distress syndrome (ARDS)³
- Pulmonary edema
 - Supplemental O₂ (for acute lung injury and non-cardiogenic pulmonary edema as needed)
 - Manage same as ARDS from any other cause: avoid intubation if possible; if intubation or sedation required, hyperventilation must be maintained
 - Pulmonary edema will improve as ASA levels fall³
- Follow arterial blood gas (ABG) every 2 hours for monitoring pH along with ASA level until both are falling and stable or improving for two consecutive checks

Gastrointestinal (GI) Decontamination

- Activated charcoal (AC): at least 1 dose of 50 g initially, then 20–60 g every 3–4 hours, if tolerated; no well-studied endpoint for stopping³; AC must be plain (cathartic-free)
- Multiple-dose charcoal has been shown to modestly decrease amount absorbed (9%–18%) in volunteers⁵
- Enteric-coated ingestions: peak concentrations occur later (10–60 hours); orogastric (OG) lavage often difficult due to size of pills and tendency to form concretions/bezoar; if excessive amounts of enteric-coated tablets are ingested, consider whole bowel

irrigation, observe for minimum of 24 hours, and follow serial serum ASA levels to ensure levels are falling³

- Whole bowel irrigation: 1–2 L of polyethylene glycol solution until rectal effluent clear; has been shown to be more effective than single-dose AC in volunteers after acute ingestion of sustained-release ASA, but no studies in toxic ingestion or compared with multidose AC⁶

Alkalinization of Serum and Urine

- Salicylic acid is a weak acid in protonated form (H^+ + salicylate⁻ → H-salicylate); goal is to drive reaction toward left (charged form): charged form less likely to penetrate CNS and less likely to be reabsorbed in renal tubules
- Urine alkalinization found to be more effective and safer than forced alkaline diuresis or forced diuresis in the treatment of mild to moderate salicylate poisoning^{3,7}
 - Urine salicylate clearance is directly proportional to urine flow rate but logarithmically proportional to urine pH³
- Recommendations for urinary alkalinization:
 - For patients with clear physical and/or laboratory manifestations of salicylate poisoning: initial bolus of 1–2 mEq/kg IV of $NaHCO_3$ followed by continuous infusion of D₅W with 3 ampules of $NaHCO_3$ at 1.5–2 times the maintenance rate to maintain urinary pH 7.5–7.55³
 - Patients with symptoms but minimal physical and laboratory findings can receive the continuous infusion portion alone³
 - Indicated for ASA levels ranging 30–60 mg/dL depending on source and for patients with any signs of salicylate toxicity when serum ASA level not immediately available³

- Goals for alkalinization:
 - Keep serum pH 7.5–7.59; consider bicarbonate for patients with pH 7.5–7.55
 - Goal urine pH is 8.0 (not always obtainable)
 - Avoid acetazolamide: will raise urine pH but lead to overall worsening systemic acidosis⁴
- Supplement potassium when $K < 4.0$, as hypokalemia interferes with efforts to alkalinize the urine³
- Frequently monitor patient course, including volume status, neurological status, serum pH and electrolytes, and urinary pH every 1–2 hours during alkalinization therapy
- Recommendations for stopping urinary alkalinization (indications are less clear):
 - Most recommendations call for continuing until serum salicylate level decreases to therapeutic range; other recommendations stop when level decreases to 35–40 or when symptoms resolve³
 - Level should be decreasing and clinical status should be improving prior to stopping
 - GI decontamination should also be complete to prevent rebound toxicity from retained bezoar

Hemodialysis Indications

- No definitive studies evaluating optimal indications for hemodialysis; however, general agreement with following:
 - Salicylate level $>100^2$; consider with level >80 mg/dL⁴
 - Salicylate level >40 – 60 for chronic ingestion²
 - Clinical status of patient deteriorates despite treatment^{3,4}
 - Renal failure/insufficiency that interferes with excretion^{3,4}
 - Fluid overload or pulmonary edema in setting of alkalinization therapy^{3,4}
 - Salicylate injury to vital organs (CNS impairment, coagulopathy, pulmonary edema)³

- Severe acid-base disturbances despite appropriate supportive care³
- Consider initiation of hemodialysis early in elderly patients, chronic ingestions, AMS, acidemia, and other severe underlying disease (congestive heart failure, chronic kidney disease)³



Patient Care Warnings

- Avoid intubation if possible; it is difficult to maintain the necessary minute ventilation to maintain the respiratory alkalosis; failure to provide goal minute ventilation will lead to worsening of acidosis and therefore increase CNS levels and toxicity of ASA
- Do not intubate because of concern that patient may fatigue; instead, wait until the patient shows signs of hypoventilation by clinical evaluation or blood gas analysis; intubate if necessary for obtundation, hypotension, hypoventilation, or severe metabolic acidosis³

References

- ③ 1. American Association of Poison Control Centers. Web site annual report 2002: www.aapcc.org.
- ③ 2. Dawson AH, Whyte IM. Therapeutic drug monitoring in drug overdose. *Br J Clin Pharmacol* 2001;52:97S-102S.
- ③ 3. Yip L, Dart RC. Concepts and controversies in salicylate toxicity. *Emerg Med Clin North Am* 1994;12: 351-64.
- ③ 4. Borkan, SC. Extracorporeal therapies for acute intoxications. *Crit Care Clin* 2002;18:393-420.
- ③ 5. Kirshenbaum LA, et al. Does multi-dose charcoal therapy enhance salicylate excretion? *Arch Intern Med* 1990;150:1281.
- ③ 6. Kirshenbaum LA, et al. Whole-bowel irrigation versus activated charcoal in sorbitol for the ingestion of modified-release pharmaceuticals. *Clin Pharmacol Ther* 1989;46:264.
- ③ 7. Prescott LF, et al. Diuresis or urinary alkalinization for salicylate poisoning? *Br Med J* 1982;285:1383.

Digoxin Toxicity

Definition, Etiology, and Epidemiology

- Incidence in 2002: 2923 cases (2035 unintentional), 154 major toxicities, 13 deaths¹
- Incidence in long-term therapeutic use is 50%, accidental large overdose 10%, and intentional overdose 40%
- Digoxin poisons the Na-K ATPase, leading to increased intracellular calcium levels
- Toxicity is an exaggeration of the drug's mechanism of action

Pearls of the History and Physical Examination

- Factors associated with increased risk of digoxin toxicity²
 - Increased age
 - Renal insufficiency (acute or chronic)
 - Underlying cardiac disease: especially cardiac amyloidosis
 - Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypercalcemia)
 - Hypothyroidism: leads to decreased clearance
 - Advanced pulmonary disease, especially cor pulmonale
 - Drug interactions increasing receptor binding or impairing clearance: quinidine, verapamil, and amiodarone
- Symptoms of toxicity^{2,3}:
 - Fatigue (95%) and anorexia (80%) early
 - Nausea and vomiting (30%-80%), dizziness, weakness (82%), malaise
 - Visual symptoms (95%), especially halos around bright lights and enhanced perception of yellow and green colors (rare)

- Rare: headache, neurological pain, confusion, syncope, abdominal pain, diarrhea, delirium, and hallucinations

Diagnostic Studies and Laboratory Values

Digoxin Level

- Digoxin is 80% bioavailable; digitoxin is 100%
- Measure 6 hours after ingestion; earlier measurements will lead to spuriously high levels as drug is still in distribution phase⁴
- Digoxin concentrations impart diagnostic and prognostic information and can define both the need for and dosage of antidotal therapy in overdose⁴
- Wide overlap between drug level and level of toxicity: therefore only a temporal relation of sign/symptoms to drug withdrawal or administration of F(ab) fragment antidigoxin antibodies is confirmatory of digoxin toxicity²

Electrocardiogram (ECG)

- Rhythm disturbances are the hallmark of digoxin toxicity, although no arrhythmia is diagnostic of digoxin toxicity; suspect digoxin toxicity in any patient on digoxin with both increased automaticity and depressed conduction (even if serum level is 1–2 ng/mL)²
- Atrioventricular (AV) junctional block of varying degrees with increased ventricular automaticity are the most common manifestations of digoxin toxicity (30%–40%)²
 - First-degree AV block is usually manifestation of digoxin effect
 - Second-degree (usually Mobitz I; Mobitz II due to digoxin toxicity is rare)
 - Third-degree block should be distinguished from apparent AV dissociation due to accelerated idioventricular or AV junctional pacemaker

- Increased frequency of premature ventricular contractions (PVCs) are the most common manifestation of increased automaticity²
- Downsloping ST segments are associated with digitalis therapy and not necessarily toxicity
- Rare arrhythmias: fascicular tachycardia, ventricular bigeminy with alternating right- and left-axis deviation, and bidirectional ventricular tachycardia are highly suggestive of digoxin toxicity²
- The development of repetitive and multiform PVCs during atrial fibrillation in a patient whose ventricular rate had previously been well controlled with digoxin is suggestive of toxicity²
- Ventricular fibrillation is rarely the first electrophysiological manifestation of digoxin toxicity²

Electrolytes

- Potassium
 - Hypokalemia worsens digoxin toxicity and may exacerbate digoxin-induced AV block
 - Hyperkalemia can be caused by massive overdoses of digoxin (usually does not occur with chronic toxicity except in setting of coexistent renal failure)²
 - Hyperkalemia may worsen conduction delay regardless of cause²
- Hypomagnesemia and hypercalcemia can worsen effects of toxicity
- Monitor creatinine because worsening renal function leads to decreased clearance

Guide to Acute Management

Gastrointestinal Decontamination

- Lavage or ipecac: if early (<1 hr) after ingestion; avoid vagal stimulation, which can worsen conduction block; some researchers recommend pretreatment with atropine³
- Charcoal effectively absorbs digoxin if given within

6–8 hours; can repeat for enterohepatic circulation (cholestyramine is alternative for activated charcoal); clinical effectiveness of either has not been established³

Correct Electrolyte Abnormalities

- Correct low potassium
 - Will improve digitalis-induced AV block, but do with caution in patients with second- or third-degree AV block as hyperkalemia can make these blocks worse²
 - Potassium is indicated for ectopic ventricular arrhythmias and may be effective even when the serum potassium concentration is in the normal range in patients with ventricular arrhythmias²
- Correct hypomagnesemia, as magnesium may suppress some of the digoxin-induced arrhythmias²
- Calcium therapy (i.e., calcium gluconate) in patients with hyperkalemia may make toxicity worse secondary to calcium load

Treatment of Rhythm Disturbances

- Occasional ectopic beats, first degree AV block, or accelerated junctional pacemaker in setting of atrial fibrillation: require only temporary drug withdrawal, ECG monitoring, and subsequent dose reduction²
- Rhythm disturbances that impair cardiac output require more active intervention
 - Sinus bradycardia, sinoatrial arrest, and AV block
 - Atropine is sometimes effective²
 - Temporary pacing may be needed²
 - May need digoxin-specific (Fab) antibody fragments³
 - Ventricular arrhythmias:
 - Digoxin-specific (Fab) antibody fragments
 - Potassium: as above
 - Lidocaine or phenytoin is most useful for digoxin-induced ventricular arrhythmias (they have little effect on SA node, SA, AV, or His-Purkinje conduction)^{2,3}

- Avoid quinidine and procainamide, as both depress AV and sinoatrial conduction and may exhibit proarrhythmic effects in digoxin-toxic arrhythmias^{2,3}
- Beta blockers may worsen AV conduction, decrease catecholamine-induced automaticity, shorten refractory periods of atrial and ventricular muscle, and slow conduction velocity; ultra-short-acting esmolol may be appropriate initially when possibility of worsening AV block or negative inotropic effect exists²
- Cardioversion: in the absence of severe digitalis-induced arrhythmias, DC cardioversion is safe, particularly at lower energy levels²; cardioversion potentially hazardous in severe arrhythmias with advanced digitalis toxicity and should be avoided if other measures are available and effective²

Digoxin-Specific (Fab) Antibody Fragments

- Prospectively shown to treat toxicity completely or partially⁵
- Indications
 - Life-threatening digitalis intoxication: sinus bradycardia, AV block, ventricular arrhythmia⁶
 - Early in course of digitalis-induced ventricular dysrhythmia, high-grade AV block (Mobitz II or third-degree block), severe hyperkalemia (potassium >5 caused by digitalis excess)⁶
 - Potentially life-threatening acute ingestions (10 mg in healthy adult, 4 mg in healthy child) in which signs of cardiac toxicity are present^{3,6}
 - Digoxin level >10 mmol/L, 6 hours after last dose, is an indication for Fab fragments (more cost-effective than prolonged monitoring)⁴
 - If index of suspicion of digoxin toxicity is sufficiently high, and the observed cardiac arrhythmia is serious, empiric Fab should be considered⁶
- Dosing: give over 30 minutes, unless cardiac arrest; then give as bolus⁶
 - Equimolar doses are recommended

- One vial of Digibind contains 40 mg of digoxin-specific antibody
- 64 mg of Fab neutralizes 1 mg of digoxin: therefore, each vial will neutralize 0.6 mg of absorbed digoxin
- Digibind dose (mg) = $64 \times \text{body load digoxin} =$
 - Body load digoxin = dose ingested $\times$ 0.8 for digoxin
= dose ingested $\times$ 1.0 for digitoxin
 - Body load digoxin = steady-state serum level (ng/mL) $\times$ 5.6 L (volume of distribution) $\times$ weight (kg)/1000
- Empiric dosing: when ingested dose is unknown and patient is exhibiting significant toxicity, 1 to 20 vials should be given for cases of acute toxicity and 6 vials for chronic toxicity⁶
- Complications
 - Potential worsening of congestive heart failure, increased ventricular rate in atrial fibrillation⁶
 - Hypokalemia: monitor closely^{2,6}
 - Allergic reactions: 0.8%⁷
 - Digoxin will unbind from antibody after a few days (unless cleared in urine); be aware of rebound toxicity in anuric or hemodialysis patients



Patient Care Warnings

- Potassium levels: hypokalemia worsens toxicity and may exacerbate AV block, but hyperkalemia can also worsen conduction delay; repletion of potassium is necessary, but proceed with caution in patients with second- or third-degree AV block as hyperkalemia can make these worse, necessitating external or transvenous cardiac pacing²
- Avoid calcium therapy for the hyperkalemic patient with digoxin toxicity, as this may increase arrhythmias

References

- ③ 1. American Association of Poison Control Centers. Web site annual report 2002: www.aapcc.org
- ③ 2. Kelly RA, Smith TW. Recognition and management of digitalis toxicity. *Am J Cardiol* 1992;69:108G-19G.
- ③ 3. Bayer MJ. Recognition and management of digitalis intoxications. *Am J Emerg Med* 1991;29-31.
- ③ 4. Dawson AH, Whyte IM. Therapeutic drug monitoring in drug overdose. *Br J Clin Pharmacol* 2001;52:97S-102S.
- ② 5. Antman EM, et al. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific fab antibody fragments. *Circulation* 1990;81:1744-52.
- ③ 6. Bolgiano EB, Barish RA. Use of new and established antidotes. *Emerg Med Clin North Am* 1994;12:317-34.
- ② 7. Hickey AR, et al. Digoxin-immune fab therapy in the management of digitalis intoxication: Safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol* 1991;17:590-98.

Tricyclic Antidepressant Intoxication

Definition, Etiology, and Epidemiology

- Tricyclic antidepressants (TCAs) are a frequently ingested substance in self-poisonings, along with acetaminophen, benzodiazepines, and alcohol¹
- Pharmacology
 - Toxicity of TCAs due to differing amounts of anticholinergic, alpha-blocking, antihistaminic, and adrenergic uptake inhibiting properties; metabolized in liver to inactive glucuronides, which are excreted in urine²
 - Rapidly and completely absorbed from gastrointestinal tract; undergo enterohepatic circulation
 - Peak serum concentration 2–8 hours after therapeutic dose but may be delayed in overdose (because of anticholinergic effects and large amount ingested)²

Pearls of the History and Physical Examination

- Dose ingested is a poor predictor of individual response because of variation in absorption and metabolism, but <20 mg/kg unlikely to be fatal or have serious complications³
- Anticholinergic signs: flushing, dilated pupils, hyperthermia, ileus, urinary retention, sinus tachycardia, dry mucous membranes and skin, and altered mental status^{2,3}
- Cardiovascular: most clinically important effect of TCA overdose and the usual cause of mortality
 - Arrhythmia: inhibits fast sodium channels, leading to prolongation of the QRS, PR, and QT intervals³
 - Hypotension: from decreased myocardial contractility and decreased peripheral vascular resistance (alpha blockade)³
- Central nervous system signs
 - Confusion, delirium, hallucinations, lethargy progressing to seizures and coma²
 - Physical examination: clonus, chorea, hyperactive reflexes, myoclonic jerks, positive Babinski's sign
 - Pyramidal signs, rigidity, ophthalmoplegia, respiratory depression³

Diagnostic Studies and Laboratory Values

- Diagnosis is clinical: drug levels have not been shown to correlate with symptoms of serious poisoning²
- Electrocardiogram (ECG): follow QRS width, continuous cardiac monitoring
 - Sinus tachycardia earliest and most common sign of toxicity²
 - Prolonged QRS: QRS width used to aid in prediction of seizure activity and ventricular arrhythmias³
 - QRS >0.1 sec: moderately predictive of seizures³
 - QRS >0.16 sec highly predictive of seizures and moderately predictive of ventricular arrhythmias³

- Bradycardia and slow idioventricular rhythm are late manifestations and harbinger of cardiac arrest²
- Other ECG findings: QT interval, AV blocks, bundle branch block, complete heart block²
- Serum electrolytes; blood, urea, nitrogen; creatinine; glucose; complete blood count; acetaminophen level; arterial blood gas test and chest x-ray for critical patients and when alkalization therapy is initiated
- Often see a mixed acidosis: metabolic and respiratory acidosis³

Guide to Acute Management

- Drug elimination: because of large volume of distribution and high protein binding, hemodialysis, forced diuresis, and hemoperfusion have no role in drug elimination³
- Patients with no major signs of toxicity, normal neurological examination result, and normal vital signs after 6 hours: repeat ECG and second dose of plain activated charcoal; if QRS duration is normal and no rightward shift in the terminal 40 ms of QRS in frontal plane and bowel sounds present, patient may be released²
- Continue to observe until sinus tachycardia resolves (possible marker of continued absorption)²

Supportive Care

- Secure airway and breathing, supplemental oxygen, continuous pulse oximetry, IV access
- Baseline ECG and continuous telemetry monitoring

Gastrointestinal Decontamination

- No induced emesis because of possibility of rapid neurological deterioration and high incidence of seizures resulting in increased risk of aspiration²

- Gastric lavage: if within 1 hour of a potentially life-threatening ingestion³
- Activated charcoal (AC) recommended for treatment of all TCA overdoses² to absorb TCAs in gut and decrease enterohepatic recirculation²
 - 1–2 g/kg body weight with cathartic (sorbitol or magnesium citrate), then repeated doses (if major signs of toxicity present) (0.5–1 g/kg) every 4–8 hours until patient improving (provided there is gut motility)²
- Shown to decrease peak plasma concentrations in healthy volunteers with therapeutic doses, but no clinical studies of overdose situations²

Sodium Bicarbonate

- For predominant effect due to sodium load but also for systemic alkalinization
- Single most effective intervention for management of TCA cardiovascular toxicity; reversal of QRS prolongation, ventricular arrhythmias, hypotension³
- Indications^{2,3}
 - pH <7.1
 - QRS >0.10 sec
 - Arrhythmias
 - Hypotension
 - Cardiac arrest
- 1–2 mEq/kg bolus, then drip solution of 150 mEq NaHCO₃ in 1 L of D₅W to maintain arterial pH of 7.5–7.55; monitor arterial pH frequently²
- Beneficial even if systemic pH already normal or alkalemic

Arrhythmias

- Sinus tachycardia generally requires no additional treatment but may be a sign of continued absorption; necessitates further monitoring
- Correct hypoxia, hypotension, and acidosis

- NaHCO_3 indicated before initiating any other antiarrhythmic drugs
 - Acute treatment with 1–2 mEq/kg for ventricular tachycardia, ventricular fibrillation, cardiac arrest; avoid antiarrhythmics if possible, given potential for inducing further arrhythmias
 - Lidocaine: drug of choice for ventricular arrhythmias^{2,3}
 - Class IA and IC antiarrhythmics are absolutely contraindicated: these exhibit the same cardiotoxic effects of TCAs^{2,3}
 - Class II is effective in reversing many arrhythmias, but side effects of beta blockers (hypotension, bradycardia, cardiac arrest) have been reported²; use only for life-threatening tachycardia after other measures have failed
- Atropine is ineffective in reversing bradydysrhythmias due to muscarinic blockade²
- Temporary pacemaker for complete heart block, Mobitz II, refractory symptomatic bradycardia²
- Cardiac arrest: occurs in 4%–12% of overdoses; follow ACLS protocol with the following caveats: NaHCO_3 early for systemic alkalinization and for sodium load; avoid class IA and IC antiarrhythmics, continue resuscitation efforts for at least 1 hour²

Seizures

- Diazepam for acute onset^{2,3}; phenobarbital as second line²
- Flumazenil is contraindicated due to increased association with seizures²
- Treat seizures aggressively because associated acidosis worsens cardiac complications²
- Prophylactic phenytoin is not recommended because its cardiac effects may lead to increased ventricular dysrhythmias²
- Agitation can be treated with IV benzodiazepines²



Patient Care Warnings

- Class IA and IC antiarrhythmics are absolutely contraindicated in TCA toxicity as these agents may potentiate the cardiotoxicity of the TCA
- Physostigmine has no role in the management of TCA overdose, despite historical use

References

- ③ 1. Pimentel L, Trommer L. Cyclic antidepressant overdoses. *Emerg Med Clin North Am* 1994;12:533-47.
- ③ 2. Kerr GW, McGuffie AC, Wilkie S. Tricyclic antidepressant overdose: Review. *Emerg Med J* 2001;18:236-41.
- ② 3. Boehnert MT, and Lovejoy FH. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *New Engl J Med* 1986;313:474-79.

Methanol Toxicity

Definition, Etiology, and Epidemiology

- Solvent in cleaning solutions, printing solutions, adhesives, enamels, stains, dyes, varnishes, thinners, paint removers, antifreeze agent in windshield-wiping fluids, fuel for camp stoves, among other sources¹
- Oral absorption is rapid; peaks at 30–60 minutes¹
- Methanol metabolized by alcohol dehydrogenase to formaldehyde and then rapidly to formic acid, which results in toxicity and anion gap acidosis¹
- Lethal dose can be as little as 30–100 mL, and lesser quantities can cause permanent blindness²

Pearls of the History and Physical Examination

- Triad of visual complaint, abdominal pain, and metabolic acidosis should always suggest methanol poisoning
- Coingestion of alcohol may delay onset of symptoms beyond 24 hours¹
- Visual disturbances: blurred vision, altered visual fields, photophobia, complete blindness; examination may reveal hyperemia of optic disk, decreased papillary responses to light, peripapillary retinal edema, edema of optic disc¹
- Central nervous system symptoms: headache, vertigo, lethargy, and confusion, with mild to moderate toxicity; occurrence of coma and convulsions with severe cases suggests cerebral edema: associated with increased mortality rate^{1,3}
- Gastrointestinal (GI) symptoms: nausea, vomiting, abdominal pain (acute pancreatitis common complication of severe toxicity)¹

Diagnostic Studies and Laboratory Values

- Anion gap acidosis
 - May not be present early or with concurrent alcohol (EtOH) ingestion (blocks EtOH dehydrogenase, thus decreasing production of formic acid)¹
 - Increased plasma osmolal gap: 1 mg/dL of methanol = 0.34 mOsm/kg H₂O; late in course, osmolal gap may resolve as methanol is converted to formic acid⁴
 - Clinical symptoms and mortality correlate more closely with extent of metabolic acidosis than methanol level¹; patients with pH <7.0 have 20 times the mortality rate of those with pH >7.0³

Guide to Acute Management

Supportive Care

- Thiamine, folate, multivitamin, glucose (give thiamine prior to any glucose administration); intravenous (IV) fluids
- Consider bicarbonate for pH <7.3 to decrease ratio of formic acid to formate¹
 - Folic or folinic acid to increase formic acid
- With high suspicion for methanol toxicity: empiric treatment with fomepizole or ethanol should begin while waiting on methanol level⁴

GI Decontamination

- Gastric lavage is advised if early in course, but no clinical evidence to support its use¹
- Activated charcoal for coingestants if present

Fomepizole

- Indications: any of these three (based on consensus opinion)¹
 - Plasma methanol concentration >20 mg/dL
 - Recent history of toxic level of ingestion and osmolal gap >10 mOsm/kg H₂O
 - History or strong clinical suspicion of methanol poisoning and two of following: pH <7.3, serum HCO₃ <20, osmolal gap >10
- No clinical data to confirm superiority of fomepizole over ethanol, but it is easier to administer, longer acting, does not require critical care support for administration, and has greater affinity for alcohol dehydrogenase than ethanol
- Data on fomepizole center on case series, retrospective analysis, and case studies^{5,6}; do not use with EtOH because prolongs half-life of EtOH

Ethanol

- Used for more than 50 years but never approved for this indication by United States Food and Drug Administration
- IV or oral: has more than a tenfold greater affinity for alcohol dehydrogenase than methanol¹
- Indications: same as for fomepizole above; not useful if late presentation, as methanol has already been metabolized¹
- Goal plasma concentration of 100–150 mg/dL¹
- Continue until serum methanol concentration is <20 mg/dL and patient is asymptomatic with normal arterial pH¹

Hemodialysis

- Use for severe intoxications to remove parent compound and metabolites
- Indications: any of the following¹:
 - pH <7.25–7.3
 - Visual signs/symptoms
 - Deteriorating vital signs despite intensive supportive care
 - Renal failure
 - Significant electrolyte disturbance unresponsive to conventional therapy
 - Serum methanol concentration >50 mg/dL^{1,5,7}
- Treat with HD until serum level less than 20¹
- Dose: adjust fomepizole and EtOH when on hemodialysis (HD)
- Continue ETOH or fomepizole for several hours after the cessation of HD to protect from potential rebound of methanol levels; monitor serum osmolality and electrolytes every 2–4 hours for 12–36 hours post HD¹
- Dialysis should be without heparin administration, given increased risk of intracranial hemorrhage due to methanol²

Ethylene Glycol Toxicity

Definition, Etiology, and Epidemiology

- Ethylene glycol is sweet-tasting substance found in antifreeze and other solvents³
- Estimated minimal lethal dose is 100 mL in adults³
- Symptoms and anion gap acidosis are due to accumulation of glycolic acid (toxic metabolite of ethylene glycol via action of alcohol dehydrogenase)³

Pearls of the History and Physical Examination

Stage 1

- First 12 hours after ingestion (longer, if coingestion of alcohol)
- Mental status depression similar to that from alcohol intoxication (due to ethylene glycol)³
- With severe cases can lead to coma, seizures, respiratory depression³

Stage 2

- 12–24 hours after ingestion
- Due to effects of glycolate, may observe acidosis, heart failure, pulmonary edema, and adult respiratory distress syndrome in severe intoxications³

Stage 3

- 24–72 hours after ingestion
- Flank pain, acute tubular necrosis, hypocalcemia, renal failure due to oxalate production, which is directly toxic to tubules and leads to intraluminal obstruction³

Diagnostic Studies and Laboratory Values

- Anion gap acidosis (may not be present with concurrent EtOH ingestion, which blocks EtOH dehydrogenase)³
- Increased plasma osmolal gap: each 1 mg/dL of ethylene glycol leads to increase in serum osmolality by 0.20 mOsm/kg H₂O⁴; late presentations may not have elevated osmolal gap because glycolic acid does not contribute to osmolal gap³
- Urine sediment: calcium oxalate crystals³
- Renal failure, hypocalcemia³
- Wood's lamp may reveal fluorescence of urine²

Guide to Acute Management

Supportive Care

- Thiamine, folate, multivitamin infusion, glucose⁴
- Intravenous fluid for hypotension⁴
- Bicarbonate for systemic pH <7.3³; also to keep urine pH >7.0 and decrease precipitation of urine calcium oxalate crystals (theoretical benefit not shown in clinical trials)⁸
- Asymptomatic hypocalcemia generally not treated due to risk of increasing the formation of calcium oxalate crystals³; seizures due to hypocalcemia should be treated first with standard anticonvulsants³
- With high suspicion for ethylene glycol toxicity: empiric treatment with fomepizole or ethanol should begin while waiting on level⁴

Fomepizole

- Antidote of choice for ethylene glycol toxicity; recently approved by United States Food and Drug Administration for this use³
- Indications for fomepizole according to 1999 practice guidelines of American Academy of Toxicology (any of the following):

- Plasma ethylene glycol concentration >20 mg/dL
- Recent ingestion of ethylene glycol and an osmolar gap >10 mOsm/kg
- High clinical suspicion and two of following: pH <7.3 , serum bicarbonate <20 mmol/L, osmolar gap >10 mOsm/kg, or urinary oxalate crystals⁹
- Shown to have dramatic improvements in acidemia and prevention of renal injury (from ethylene glycol)
- No benefit late in poisoning when ethylene glycol has already been metabolized to its toxic metabolite⁴

Ethanol

- Ethanol has more than two orders of magnitude of affinity for alcohol dehydrogenase than ethylene glycol⁸

Hemodialysis

- Indicated in severe intoxications to remove parent compound and metabolites
- Indications
 - Ethylene glycol level >50 mg/dL was formerly considered an indication for hemodialysis⁷; however, patients with normal renal function and no acidosis may be treated with fomepizole alone, along with close monitoring of renal function^{3,10}
 - Patients who have or are likely to develop major sequelae of ethylene glycol ingestion including³:
 - Metabolic acidosis (pH <7.3)
 - Deterioration of clinical status with respiratory failure or hypotension
 - Acute renal failure and a metabolic derangement that is unresponsive to standard therapy
- Continue hemodialysis until levels <20 mg/dL, acidosis has resolved, and no signs of systemic toxicity

Other

- Pyridoxine (50 mg QID) and thiamine (100 mg QID) for 2 days can promote conversion of glyoxylate into nontoxic end products: not a proven therapy⁸

Isopropyl Alcohol Toxicity

Definition, Etiology, and Epidemiology

- Found in rubbing alcohol (usually 70% isopropyl), de-icers, other solvents^{3,4}
- Compound itself is odorless and bittersweet^{3,4}
- Quickly and completely absorbed with peak levels in 15–30 minutes³
- Metabolized by alcohol dehydrogenase to acetone, which is excreted by kidneys; however, it is the parent compound that is toxic in this ingestion³
- Half-life of isopropanol is 3–7 hours but is prolonged with ethanol coingestion³

Pearls of the History and Physical Examination

- Toxic clinical effects are due to the isopropyl³
- Acetone causes only mild central nervous system (CNS) depression³
- CNS effects: ataxia, confusion, stupor, lethargy; can progress to coma³
- Nausea, vomiting, abdominal pain, and gastritis³
- Acetone on breath: fruity odor³
- Hypotension or shock secondary to myocardial depression and vasodilatation seen with severe ingestions.
 - Hypotension and coma are strong predictors of mortality^{2,3}

Diagnostic Studies and Laboratory Values

- Plasma level >100 mg/dL can cause coma⁴
- Plasma level of 400 mg/dL is life-threatening, but presence/absence of clinical signs and symptoms (especially hypotension) is more reliable prognostically²
- Can cause hypoglycemia from interference of gluconeogenesis by isopropanol³
- Can confirm diagnosis and follow course with plasma isopropanol levels¹

Guide to Acute Management

- No role for ethanol or fomepizole because it is the parent compound that is toxic in this case and, therefore, isopropyl metabolism is desired³

Supportive Care

- Intravenous fluids and vasoconstrictors as needed for hypotension³
- Airway protection as needed

Gastrointestinal Decontamination

- Utility limited because of rapid and complete absorption, but gastric lavage to remove residual isopropanol is suggested²

Hemodialysis

- Removes acetone and isopropanol efficiently³
- Indications
 - Hypotension^{2,3}
 - Plasma levels >400 mg/dL^{2,3}
 - Underlying hepatic or renal insufficiency, which limits metabolism and excretion of isopropanol
 - Significant CNS depression³

- Reasonable to empirically dialyze a patient with deteriorating clinical status and unexplained osmolar gap until a serum assay excludes isopropanol ingestion²



Patient Care Warnings

- Ethanol and, more recently, fomepizole have been used with methanol and ethylene glycol toxicity because they limit metabolism to toxic metabolites
- Ethanol and fomepizole have *no* place in treating isopropyl toxicity because it is the parent compound that is toxic; therefore, metabolism is encouraged
- In all three ingestions, hemodialysis has a role in removing parent compound and metabolites

References

- ③ 1. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *Clin Toxicol* 2002;40:415-46.
- ③ 2. Borkan SC. Extracorporeal therapies for acute intoxications. *Crit Care Clin* 2002;18:393-420.
- ③ 3. Abramson S, Singh A. Treatment of the alcohol intoxications: Ethylene glycol, methanol, and isopropanol. *Curr Opin Nephrol Hypertension* 2000;9:695-701.
- ③ 4. Burkhart K, Kulig K. The other alcohols: Methanol, ethylene glycol, and isopropanol. *Emerg Med Clin North Am* 1990;8: 913-28.
- ③ 5. Megarbane B, et al. Treatment of acute methanol poisoning with fomepizole. *Intensive Care Med* 2001;1370-78.
- ③ 6. Brent J, et al. Fomepizole for the treatment of methanol poisoning. *New Engl J Med* 2001;344:424-29.
- ③ 7. Dawson AH, Whyte IM. Therapeutic drug monitoring in drug overdose. *Br J Clin Pharmacol* 2001;52:97S-102S.
- ③ 8. Davis DP, et al. Ethylene glycol poisoning: Case report of a record-high level and a review. *J Emerg Med* 1997;15:653-67.

- ③ 9. Barceloux DG, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning: Ad Hoc Committee. Clin Toxicol 1999; 37:537-60.
- ② 10. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. Ann Pharmacother 2002;36:1085-89.

Alcohol Withdrawal

Definition, Etiology, and Epidemiology^{1,2}

- There are an estimated 8 million people in the United States with alcohol dependence and approximately 500,000 episodes of alcohol withdrawal each year requiring pharmacological management
- The central nervous system adapts to chronic substance use; *tolerance* is the increasing use of the substance to produce the same effects that were previously attained
- *Withdrawal* is the clinical syndrome that ensues upon cessation of the substance in a patient who has adapted to the effects of the agent; withdrawal from different substances can have specific clinical syndromes
- Pathophysiology: alcohol and other sedatives such as benzodiazepines bind to the receptor for the main inhibitory neurotransmitter in the central nervous system, gamma-aminobutyric acid (GABA), leading to the clinical effect of sedation. With chronic use, there is downregulation of GABA receptors to compensate for the chronic sedating effect, leading to an overall inhibitory tone in the neurons involved
- Upon withdrawal of the sedating agent, the GABA receptors remain downregulated, resulting in unopposed excitatory stimulation of the neurons and the clinical syndrome of withdrawal

Pearls of the History and Physical Examination^{1,2}

- Clinical history is important as symptoms generally peak approximately 72 hours from last alcohol use
- Assess for evidence of chronic alcohol use and/or dependence; simplified CAGE assessment: **C**an you cut down on your drinking? **A**re you annoyed when asked to stop drinking? Do you feel **G**uilty about your drinking? Do you need an **E**ye-opener when you get up in the morning?
- Assess for other substance abuse concurrent with alcohol use
- Presentation often divided into four syndromes based on symptoms and onset after last drink

Syndrome	Onset After Last Drink	Symptoms
Minor withdrawal	6–36 hr	Tremulousness, anxiety, diaphoresis, headache, nausea and vomiting
Alcohol seizures ("rum fits")	7–48 hr	Tonic-clonic activity and usually single; status epilepticus rare
Alcoholic hallucinosis	7–48 hr	Most often auditory but also visual and tactile
Delirium tremens (DT)	48–72 hr	Delirium, tachycardia, hallucinations, hypertension, fever, diaphoresis, hyperventilation

- DT is a true medical emergency with an associated mortality of close to 5%; risk factors for development of DT include³: history of sustained drinking, prior episode(s) of DT, age >30 years, and greater length of time from last drink to presentation
- Other signs and symptoms include:
 - Jaundice and right upper quadrant pain with associated hepatitis

- Spider angiomas, palmar erythema, gynecomastia, testicular atrophy with chronic liver disease
- Gastrointestinal bleeding from esophageal varices
- Abdominal pain from pancreatitis
- Enlarged parotid glands

Diagnostic Studies and Laboratory Values

- Elevated liver function tests with mild aspartate amino transferase and amino alanine transferase elevation often in 2:1 ratio; elevation in gamma glutamyl transpeptidase out of proportion to alkaline phosphatase
- Hyponatremia (beer potomania), hypokalemia, hypomagnesemia
- Elevated lipase and amylase from concurrent pancreatitis
- Thrombocytopenia, anemia from alcohol-induced bone marrow suppression; elevated mean corpuscular value (MCV)
- Respiratory alkalosis from hyperventilation
- Elevated creatine kinase from seizure activity and hyperthermia/tremulousness
- Urine toxicology screen for polysubstance use
- Urine ketones secondary to alcohol use and poor nutrition
- Withdrawal is a diagnosis of exclusion; evaluation of other causes for symptoms described should also be undertaken with central nervous system imaging and lumbar puncture as indicated

Guide to Acute Management

Supportive Care

- Thiamine, folate, multivitamin, glucose (give thiamine before any glucose administration)
- Intravenous fluids (typically isotonic) to replete volume and maintain euvolemia

- Replete electrolytes as indicated
- Frequent reevaluation for adequacy of therapy

Pharmacological Management^{1,4}

- Benzodiazepines are the mainstay of therapy
- Treatment involves substituting a long-acting agent for the abused drug then gradually tapering the dosage
- “Symptom-triggered” therapy most commonly employed: patient receives medication when symptoms exceed a threshold of severity

Presentation	Therapy
Low risk of DT	Chlordiazepoxide 25 mg: 50 mg po when the score of symptoms ≥ 8 on Clinical Institute Withdrawal Assessment for Alcohol Scale <CIWA-Ar (see Appendix 1); reassess every 4 hours, with goal a score <8 on two consecutive assessments
Prior history of DT or other risk factors (see above)	Chlordiazepoxide 25 mg: 50 mg po q 6 hours, tapering over next 4–7 days; additional 25 mg: 50 mg po when the score of symptoms ≥ 8 on CIWA-Ar when reevaluating every 4 hours
DT	Diazepam 5–10 mg IV or lorazepam 1–2 mg q 5 min until calm but alert state achieved; continue until patient no longer delirious and can safely take po medication without risk of aspiration; may require scheduled dosing of parenteral benzodiazepines or continuous infusion
Refractory DT	Propofol or phenobarbital for symptoms refractory to benzodiazepines; requires endotracheal intubation and mechanical ventilation
Withdrawal seizures	Carbamazepine has been used effectively in withdrawal seizures; often respond to benzodiazepines alone



Patient Care Warnings

- Give thiamine to the chronic alcoholic before any glucose administration
- Withdrawal is a diagnosis of exclusion, and evaluation of other causes for such presentation should also be undertaken
- Frequent reevaluation and therapeutic changes are necessary to prevent development of DT

References

- ③ 1. Kosten T, O'Connor P. Management of drug and alcohol withdrawal. *N Engl J Med* 2003;348:1786-95.
- ③ 2. Olmed R, Hoffman R. Withdrawal symptoms. *Emerg Med Clin North Am* 2000;18:273-88.
- ③ 3. Ferguson JA, et al. Risk factors for delirium tremens development. *J Gen Intern Med* 1996;11:410-14.
- ③ 4. Holbrook A, et al. Diagnosis and management of alcohol withdrawal. *Can Med Assoc J* 1999;160:675-80.

PA CATHETERS

Definition, History, and Data

- Right-heart catheterization and the first measurements of pulmonary artery (PA) wedge pressure began in the mid 1940s; they were restricted initially to the catheterization laboratory.
- In 1970 Swan and Ganz introduced balloon-tipped flotation, enabling bedside PA catheterizations¹
- Retrospective analysis has shown increased mortality rates and hospital stays associated with PA catheterization²
- Randomized clinical trials are currently under way to investigate PA catheter use and its effect on clini-

cal outcomes, including mortality in refractory congestive heart failure (CHF) and in acute lung injury/adult respiratory distress syndrome (ARDS), in an attempt to justify use and safety in certain patient populations

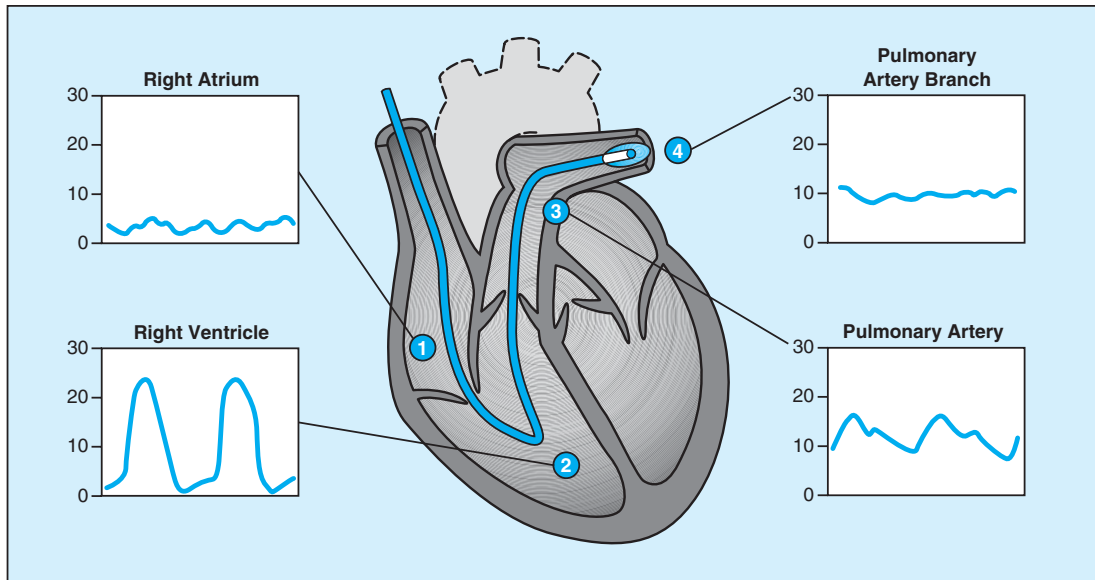
Indications

- PA catheters historically used for¹:
 - Diagnosis of complications of myocardial infarction, pulmonary edema (cardiogenic vs. noncardiogenic), cardiac tamponade, and cause of hypotension, shock, or renal failure
 - Management of advanced CHF, shock, high-risk surgery patients or for postoperative complications, assessment of intravascular volume/left-sided filling pressures, and assessment of response pharmacological therapy (pulmonary hypertension/heart failure)

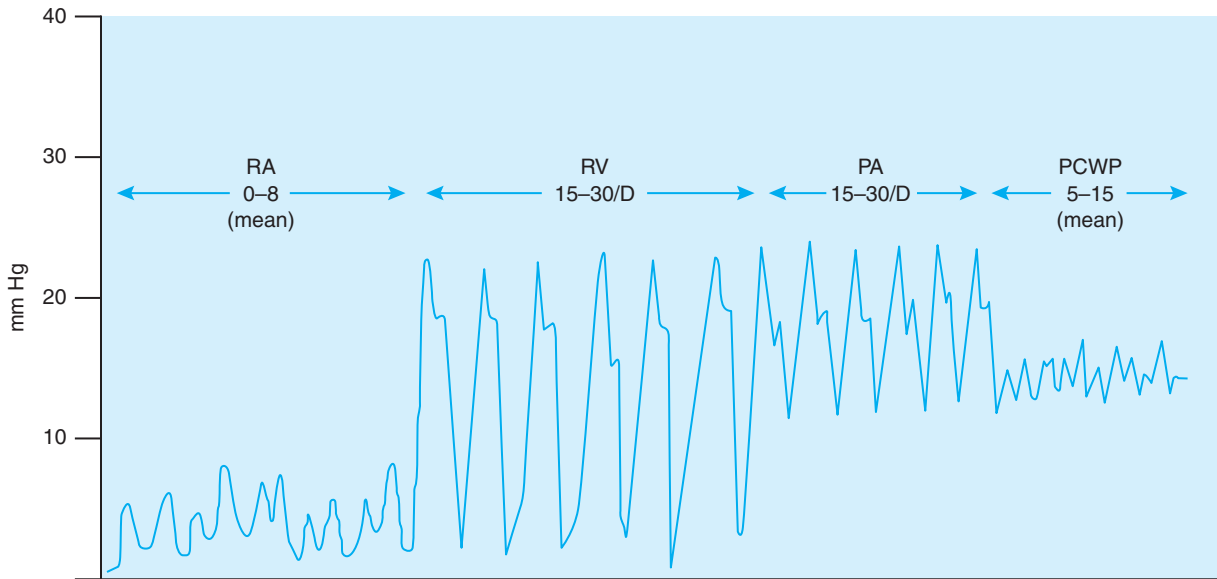
Interpretations of Waveforms

Right Atrial (RA) Waveforms

- Normal pressure 0-8 mm Hg
- A wave: atrial contraction (follows P wave on ECG rhythm strip)
 - Cannon A waves = AV dissociation: atria contracts against closed tricuspid valve
- C wave is sometimes seen immediately following A wave: it represents upward movement of tricuspid valve during ventricular contraction (corresponds to QRS on ECG)
- X descent: atrial relaxation; follows A wave on ECG
- V wave: atrial filling against a closed tricuspid valve (follows T wave)
 - Prominent V waves are seen with tricuspid regurgitation



Normal pressures and waveforms obtained as a pulmonary artery flotation catheter is advanced from the right atrium to a pulmonary artery wedge position. (Adapted from Morgan GE, Mikhail MS. *Clinical Anesthesiology*. Appleton & Lange, 1992; and Marino PL. *The ICU Book*, 2nd ed. Williams & Wilkins, 1998, p 157.)



- Y descent: rapid atrial emptying secondary to tricuspid valve opening
 - Rapid X and Y descents are a clue to constrictive pericarditis

Right Ventricular (RV) Waveforms

- Normal pressure is 15-35 mm Hg systolic and 0-8 mm Hg diastolic
- RV systolic pressure should equal pulmonary artery (PA) systolic pressure except with pulmonic valve stenosis or RV outflow obstructions

PA Waveforms

- Systolic peak (corresponds to T wave on ECG) with a dicrotic notch (pulmonic valve closure) and a diastolic trough.
- Normal pressures are 15-25 mm Hg systolic, 8-15 mm Hg diastolic
- In normal conditions PA diastolic is 1-3 mm Hg greater than pulmonary artery wedge pressure (PAWP)
- In conditions where PVR is increased (e.g., ARDS, hypoxia, fibrosis, pulmonary hypertension), the difference between PA diastolic and PAWP can be much greater; therefore, PA diastolic pressure is not an accurate marker of wedge pressure

PAW Waveforms

- Normal 2-12 mm Hg
- PCWP tracing has same A,V waves and X,Y descents as in RA pressure tracing
 - Mitral regurgitation will have prominent V waves
- PAWP should be measured at end-expiration (for ventilated and nonventilated patients)
- For accurate wedge, balloon tip should be in lung zone III (dependant portions) to ensure a continu-

ous column of blood from LA to balloon; flow-directed catheters ideally go to lung zone III on their own

- Lung zone I: superior parts of lung; have less circulation and capillary pressure is always less than positive end-expiratory pressure (PEEP); therefore no continuous column of blood
- Lung zone II: middle portions of lung; capillary pressure is intermittently obstructed by alveolar pressure (especially late in diastole)
- Lung zone III: goal location; capillary pressure is continuously greater than alveolar pressure, so a continuous column of blood is always present between LA and PAWP; thus, PAWP is a better marker of LA pressure in this lung zone
- Overriding concept: $PAWP \sim LA \text{ pressure} \sim LVED \text{ pressure} \sim LVED \text{ volume/preload}^3$
 - Conditions where PAWP underestimates LVEDP⁴
 - Aortic insufficiency, pneumonectomy, pulmonary embolus, decreased LV compliance
- Conditions where PAWP overestimates LVEDP⁴
 - Increased intrathoracic pressure (positive pressure ventilation, PEEP), non-zone III placement (see below), tachycardia, mitral valve disease (thrombosis, stenosis, insufficiency), chronic obstructive pulmonary disease, pulmonary hypertension, pulmonary vein disorders (tumor, fibrosis, thrombosis, acute lung injury/ARDS⁵)
 - PEEP will affect PAWP, but effects are variable depending on clinical situation
 - If PA diastolic pressure is less than PAWP or change in PAWP is greater than a change in PEEP, balloon is probably not in zone III
 - A supine lateral x-ray can be used to verify placement of position below the heart (and, therefore, in zone III)

Measuring Cardiac Output: Two Methods

- Thermodilution¹
 - Cold saline is injected just proximal to the RA, and the temperature is sampled in the PA near the tip of the PA catheter
 - A temperature curve is generated, and the area under the curve is integrated to determine a cardiac output ($\text{area} \propto 1/\text{CO}$) (cardiac output)
 - The sooner and sharper the temperature change (smaller area), the higher the CO
 - The later and more gradual temperature change (larger area), the lower the CO
 - Potential problems and/or inaccuracies with thermodilution technique¹
 - Decreased amount of injectate → overestimates CO
 - Cooler injectate → overestimates CO
 - High rates of current intravenous fluid administration can overestimate or underestimate CO
 - Ice-cold injectate can briefly stun the heart, decreasing CO by 10%
 - Tricuspid regurgitation will generally underestimate CO
 - Intracardiac shunts will not allow accurate measurement of left-sided CO → overestimates CO
 - Very low CO and atrial arrhythmias can increase variability
- Fick equation: $\text{CO} = V_{\text{O}_2} / (\text{Ca}_{\text{O}_2} - \text{C}_{\text{VO}_2}) = V_{\text{O}_2} / (13.4 * \text{Hb} * (\text{Sa}_{\text{O}_2} - \text{S}_{\text{VO}_2}))$
 - V_{O_2} = oxygen consumption: can be measured but generally assumed to be constant at 125 mL/min = for a 70-kg patient
 - Ca_{O_2} = oxygen content of arterial blood
 - C_{VO_2} = oxygen content of venous blood
 - $\text{Ca}_{\text{O}_2} - \text{C}_{\text{VO}_2} = 13.4 * \text{Hb} (\text{g/dL}) * (\text{Sa}_{\text{O}_2} - \text{S}_{\text{VO}_2})$
 - Sa_{O_2} = arterial oxygen saturation
 - S_{VO_2} = mixed venous arterial oxygen saturation;

measured from PA port blood gas (or saturation monitor if available)

- Problems and inaccuracies of the Fick equation¹
 - Major inaccuracy centers around the value chosen for oxygen consumption term: can be measured with Douglas bag method but is cumbersome and not easily done in the intensive care unit (ICU) setting
 - Patients in an ICU setting can have quite different oxygen consumptions depending on concurrent illnesses
 - If the $S_{aO_2} - S_{vO_2}$ gradient is normal (normal S_{vO_2} ranges 70%-75%), this suggests an appropriate CO for that patient's metabolism
 - The S_{vO_2} can be followed as a surrogate marker for relative changes in the CO as long as the oxygen consumption is stable (the lower the S_{vO_2} , the lower the CO as more oxygen extracted by peripheral tissue)

Insertion

- Central venous access is obtained with a dilator sheath
- The PA catheter is inserted via the sheath; right internal jugular vein and left subclavian positions are generally easiest for PA catheter insertion due to natural curved path to PA
- Once advanced 12-15 cm, inflate balloon and continue advance, monitoring waveforms
- Once wedged, deflate balloon, and make sure PA tracing is seen; balloon should wedge with approximately 1.25 mL of air
- Transducer needs to be zeroed in relation to patient's phlebostatic axis (fourth intercostal space between the front and back of the patient's chest)⁶
- Deflate balloon when not measuring pressure; catheter should not be left in wedged position

Complications

Insertion

- Pneumothorax (1%-2%), arterial injury related to central venous access
- Arrhythmias
- Complete heart block (CHB): increased incidence in patients with LBBB (but mainly with new LBBB); overall incidence with old or indeterminate-age LBBB is very low; therefore, routine placement of temporary transvenous pacemaker for these patients is not recommended; no consensus in patients with new LBBB^{7,8}
- Catheter knotting: once in RV, usually only 15 cm further is needed to wedge (excess catheter can form loop in large RV and lead to knotting)

Continued Use

- Pulmonary infarction: occurs with prolonged wedge position; daily chest x-ray and follow waveforms to evaluate for distal migration
- PA rupture: incidence 0.2% but mortality nearly 50%¹
- Infection: line sepsis (0.3%-0.5% per day per catheter),⁹ endocarditis; prospective study comparing changing PAC lines at 4- vs. 7-day intervals found no statistically significant difference in catheter-related infections, but a trend toward more infections in the 7-day group^{10,11}
- Thrombosis/embolism

Misinterpretation and Misapplication of Data

- Main source of morbidity and associated mortality rates of PA catheters
- Multicenter study in 1990 showed 47% of clinicians could not determine wedge pressure⁵
- Studies of supranormalization of hemodynamic parameters have generally resulted in higher mortality and morbidity rates³

References

- ③ 1. Cruz, Franklin. The pulmonary artery catheter: Uses and controversies. *Crit Care Clin* 2001;17:271-91.
- ③ 2. Gore, et al. A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocardial infarction. *Chest* 1987;92:721-27.
- ③ 3. Williams, et al. Pulmonary artery catheter. *Curr Opin Crit Care* 2002;3:251-56.
- ③ 4. Brandstetter, et al. Swan-Ganz catheter: Misconceptions, pitfalls, and incomplete user knowledge—an identified trilogy in need of correction. *Heart Lung* 1998;27:218-22.
- ② 5. Fang, et al. Starling resistor effects on pulmonary artery occlusion pressure in endotoxin shock provide inaccuracies in left ventricular compliance assessments. *Crit Care Med* 1996;24:1618-25.
- ③ 6. Rapoport, et al. Patient characteristics and ICU organizational factors that influence frequency of pulmonary artery catheterization. *JAMA* 2000;283:2559-67.
- ② 7. Shasby, et al. Swan-Ganz catheter location and left atrial pressure determine the accuracy of the wedge pressure when positive end-expiratory pressure is used. *Chest* 1981; 80:666-70.
- ② 8. Morris, et al. Risk of developing complete heart block during bedside pulmonary artery catheterization in patients with LBBB. *Arch Intern Med* 1987;147.
- ③ 9. Amin DK, Shah FK, Swan HJC. The techniques of inserting a Swan-Ganz catheter. *J Crit Illness* 1993;8:1147-56.
- ② 10. Eyer, et al. Catheter-related sepsis. *Crit Care Med* 1990;18: 1073-79.
- ③ 11. Chen, et al. Comparison between replacement at 4 days and 7 days of the infection rate for pulmonary artery catheters in the intensive care unit. *Crit Care Med* 2003;31:1353-58.

CRITICAL CARE PHARMACOLOGY

Amiodarone (Cordarone)—IV Use¹

- Use/indications: refractory ventricular arrhythmias, prophylaxis or rate control of supraventricular arrhythmias when other agents are inappropriate or ineffective
- Pharmacological effects: class III antiarrhythmic agent but has properties of all four classes

- Clinical effects: prolongs intranodal conduction and refractoriness of atrioventricular (AV) node, coronary vasodilation, hypotension
- Dosing: 150-mg bolus over 10 minutes, then 1 mg/min for 6 hours, then 0.5 mg/min for 18 hours; re-bolus 150 mg for breakthrough arrhythmias (for pulseless ventricular tachycardia [VT] or ventricular fibrillation [VF], use 300 mg intravenous [IV] push per ACLS guidelines)
- Pharmacokinetics: half-life ($T_{1/2}$): 15-100 days, onset minutes, duration several months at steady state
- Contraindications: severe sinus node dysfunction
- Side effects: hyper/hypothyroidism, dose-related pulmonary fibrosis, corneal microdeposits, blue-grey skin pigmentation, bradycardia, AV block, rarely proarrhythmic, liver function test (LFT) abnormalities, hypotension

Diltiazem (Cardizem, Tiazac)—IV Use¹

- Use/indications: atrial fibrillation or flutter with rapid ventricular response, paroxysmal supraventricular tachycardia (PSVT)
- Pharmacological effects: calcium channel blocker, inhibits AV node
- Clinical effects: increased AV nodal blockade, dilation of coronary and systemic arteries, decrease in total peripheral resistance, decreased blood pressure, decreased afterload
- Dosing: bolus 0.25 mg/kg (approximately 20 mg) over 2 minutes; may repeat in 15 minutes with 0.35 mg/kg if needed; continuous infusion at 5-15 mg/hr; infusions longer than 24 hours not recommended
- Pharmacokinetics: $T_{1/2}$ 3-6 hours, onset 3 minutes, duration 1-3 hours after single dose, up to 10 hours following infusion

- Contraindications: Wolf-Parkinson-White syndrome, sick sinus syndrome, Lown-Ganong-Levine syndrome, hypotension, acute myocardial infarction with pulmonary edema, second- or third-degree AV block (without pacer in place)
- Side effects: arrhythmias, heart failure

Dobutamine (Dobutrex)¹

- Use/indications: decompensated low output heart failure, cardiogenic shock
- Pharmacological effects: beta-1 > beta-2 agonist
- Clinical effects: increases contractility, and vasodilation leads to increased cardiac output and reduced systemic vascular resistance (SVR)
- Dosing: 2.5-20 $\mu\text{g/kg/min}$ (maximum is 40 $\mu\text{g/kg/min}$); titrate dose based on desired clinical effects; minimal additional benefit over 10-15 $\mu\text{g/kg/min}$
- Pharmacokinetics: $T_{1/2}$ and onset are 1-2 minutes; duration is 10 minutes but may be prolonged following continuous infusion
- Contraindications: idiopathic hypertrophic subaortic stenosis, atrial fibrillation, atrial flutter, hypersensitivity to sulfites (preparation contains these)
- Side effects: ectopy, increased heart rate, angina, rapid ventricular response in setting of atrial fibrillation/flutter, ventricular tachycardia at higher doses

Dopamine (Intropin)¹

- Use/indications: cardiogenic shock, septic shock; bradycardia or heart block unresponsive to atropine or pacing (investigational/unlabeled use)
- Pharmacological and clinical effects: dose-dependent:
 - Low dose (0.5-2 $\mu\text{g/kg/min}$) stimulates dopamine receptors, leading to increased renal and splanchnic blood flow; low-dose dopamine has been shown to increase renal blood flow and urine

output, but outcome studies do not show a mortality benefit or benefit in terms of recovery of renal function²⁻⁴

- Moderate dose (2-10 $\mu\text{g/kg/min}$): stimulates beta-1 receptors in addition to above, leading to increasing cardiac output without increasing SVR
- High dose ($>10 \mu\text{g/kg/min}$): acts primarily as an alpha-1 agonist, leading to increased SVR and renal vasoconstriction
- Dosing: 0.5-20 $\mu\text{g/kg/min}$; titrate based on desired clinical effects rather than on different dosing ranges above
- Pharmacokinetics: $T_{1/2}$ 2 minutes, onset 5 minutes, duration 10 minutes
- Contraindications: tachyarrhythmias, pheochromocytoma
- Side effects: tachycardia, arrhythmias, ectopy, nausea, vomiting, polyuria, necrosis at injection site

Epinephrine¹

- Use, indications, and dosing:
 - Cardiac arrest: IV infusion at 1 $\mu\text{g/min}$, increasing to 3-4 $\mu\text{g/min}$; 1-mg bolus every 3 minutes per ACLS guidelines
 - Symptomatic bradycardia: IV infusion at 1 $\mu\text{g/min}$, titrating to 2-10 $\mu\text{g/min}$ (for bradycardia unresponsive to atropine or pacing)
 - Severe asthma: 0.3-0.5 mg (1:1000) subcutaneous; may repeat every 20 minutes for 3 doses
 - Anaphylaxis: 0.2-0.5 mg (1:1000) subcutaneous; may repeat every 30 minutes
- Pharmacological effects: direct-acting alpha- and beta-adrenergic activity leading to vasoconstriction
- Pharmacokinetics: onset 3-10 minutes, duration of bolus dosing is several hours
- Side effects: tachycardia, hypertension, arrhythmias, vasoconstriction

Esmolol (Brevibloc)¹

- Use/indications: supraventricular tachycardia, need for short-acting beta blockade, peri/postoperative hypertension (poor agent for general treatment of hypertension/hypertensive urgency/emergency); adjunctive agent in hypertensive emergency to block tachycardic response to primary antihypertensive treatment (i.e., with nitroprusside in treatment of aortic dissection)
- Pharmacological effects: competitive selective beta-1 blockade
- Clinical effects: negative chronotropic and inotropic activity; decreased cardiac output
- Dosing: maintenance range 50-200 $\mu\text{g/kg/min}$; initial bolus necessary for immediate effects (500 $\mu\text{g/kg}$ over 1 minute); may need repeat bolus when increasing infusion rate; titrate to clinical response
- Pharmacokinetics: $T_{1/2}$ 4-9 minutes, onset immediate with bolus dosing (30 minutes to steady state without bolus dosing), duration 10-30 minutes
- Contraindications: cardiogenic shock, acute bronchospasm, bradycardia
- Side effects: hypotension, nausea, bronchospasm, AV block

Isoproterenol (Isuprel)¹

- Use/indications: ventricular arrhythmias due to AV nodal block, Adams-Stokes syndrome, cardiac arrest, carotid sinus hypersensitivity, shock, temporary control of third-degree AV block while awaiting pacer (fifth-line agent for bradycardia/AV block: after atropine, pacing, dopamine, and epinephrine)
- Pharmacological effects: nonselective beta agonist
- Clinical effects: positive chronotropic and inotropic effect, increases myocardial oxygen consumption,

shortens conduction time and refractory period of the AV node, increases rate and strength of ventricular contractions

- Dosing: 20-60- μ g bolus, then 2-20 μ g/min; or 200 μ g SQ or IM
- Pharmacokinetics: $T_{1/2}$ 3-7 minutes, onset immediate, duration 8-50 minutes (dose-dependent)
- Contraindications: angina, tachyarrhythmias, digitalis-induced tachycardia or heart block, ventricular arrhythmia requiring inotropic therapy
- Side effects: chest pain, arrhythmia, tachycardia (caution: highly proarrhythmic)

Labetolol (Trandate, Normodyne)— IV Formulations and Uses¹

- Use/indications: hypertensive emergency, pheochromocytoma, clonidine withdrawal hypertension
- Pharmacological effects: blocks alpha, beta-1, and beta-2 receptors
- Clinical effects: vasodilation and decreased SVR, leading to lowered blood pressure (BP) without substantial decrease in heart rate, cardiac output, or stroke volume
- Dosing: 20-80 mg IV over 2 minutes; may repeat every 15 minutes (up to 300 mg), then maintenance infusion of 0.5-2 mg/min; titrate to goal reduction in BP, switch to oral when diastolic BP is 10 mm Hg above goal
- Pharmacokinetics: $T_{1/2}$ 2.5-8 hours; onset 5 minutes (IV), duration 3-6 hours; up to 18 hours after multiple boluses
- Contraindications: cardiogenic shock, uncompensated heart failure, reactive airways disease, severe bradycardia, heart block
- Side effects: orthostatic hypotension (common with IV use), dizziness, ventricular arrhythmias

Milrinone (Primacor)

- Use/indications: acute decompensated heart failure
- Pharmacological effects: inhibits cyclic AMP (cAMP) phosphodiesterases in cardiac and vascular muscle
- Clinical effects: improves diastolic function; improves contractility, leading to increased cardiac output, decreased pulmonary capillary wedge pressure (PCWP), and SVR; these changes lead to a mild increase in heart rate without an increase in myocardial oxygen consumption
- Dosing: 50 $\mu\text{g}/\text{kg}$ over 10 minutes, maintenance infusion 0.25-0.75 $\mu\text{g}/\text{kg}/\text{min}$ (reduce maintenance dose with renal insufficiency); omission of loading dose may decrease incidence of arrhythmias
- Pharmacokinetics: $T_{1/2}$ 2 hours, onset minutes, duration 3-5 hours
- Contraindications: valvular heart disease; caution: may worsen outflow tract obstruction in hypertrophic subaortic stenosis
- Side effects: ventricular arrhythmias, supraventricular tachycardia, diarrhea, blurred vision, syncope, hypotension

Nesiritide (Natrecor)

- Use/indications: acutely decompensated heart failure
- Pharmacological effects: B-type human natriuretic peptide; acts as a vasodilator by binding to guanylate cyclase receptor on vascular smooth muscle and endothelial cells
- Clinical effects: dose-dependant decrease in PCWP and systemic blood pressure; can augment diuresis
- Dosing: initial 2- $\mu\text{g}/\text{kg}$ bolus, then continuous infusion at 0.01 $\mu\text{g}/\text{kg}/\text{min}$; in selected patients, with close hemodynamic monitoring, can increase infusion rate by 0.005 $\mu\text{g}/\text{kg}/\text{min}$ every 3 hours following rebolus of 1 $\mu\text{g}/\text{kg}/\text{min}$; maximum is 0.03 $\mu\text{g}/\text{kg}/\text{min}$

- Pharmacokinetics: $T_{1/2}$ 18 minutes, onset 15 minutes, duration 1 hour
- Contraindications: cardiogenic shock (when used as sole therapy), hypotension (SBP <90 mm Hg), significant valvular stenosis, restrictive or obstructive cardiomyopathy
- Side effects: hypotension (hold infusion, may attempt to restart at lower dose without bolus), increased serum creatinine; limited experience with infusions greater than 48 hours: use with caution

Nicardipine (Cardene)¹

- Use/indications: hypertensive emergency, perioperative hypertension
- Pharmacological effects: dihydropyridine calcium channel blocker
- Clinical effects: coronary and peripheral vasodilation; dose-related increase in cardiac output, increased heart rate with decreased mean arterial pressure (MAP); may produce a negative effect on contractility in patients with severe heart failure
- Dosing: initial 5 mg/hr, titrate by 2.5 mg/hr every 5-15 minutes to maximum of 15 mg/hr
- Pharmacokinetics: $T_{1/2}$ 2-8 hours, onset 1 minute, duration 3 hours
- Contraindications: severe aortic stenosis, hypotension, cardiogenic shock, ventricular tachycardia
- Side effects: flushing, peripheral edema, headache, palpitations, rebound tachycardia

Nitroglycerine—IV Use

- Use/indications: refractory or unstable angina, congestive heart failure especially associated with acute myocardial infarction, pulmonary edema, perioperative hypertensive emergency (especially cardiovascular surgeries)

- Pharmacological effects: converted to nitric oxide in vascular tissue; leads to vascular relaxation
- Clinical effects: vasodilation venous > arterial (preload reduction at lower doses, preload and afterload reduction at higher doses >100 $\mu\text{g}/\text{min}$)
- Dosing: start at 5-10 $\mu\text{g}/\text{min}$, increase by 5-10 $\mu\text{g}/\text{min}$ every 3-5 minutes; titrate to clinical effects or to 10% reduction in MAP when giving for chest pain; maximum 200 $\mu\text{g}/\text{min}$
- Pharmacokinetics: $T_{1/2}$ 90 seconds, onset immediate, duration 15 minutes
- Contraindications: right ventricular infarction, angina secondary to hypertrophic obstructive cardiomyopathy, use of sildenafil
- Side effects: headache (common), hypotension, methemoglobinemia, thrombocytopenia, bradycardia, syncope, reflux esophagitis, tolerance

Nitroprusside (Nipride)

- Use/indications: hypertensive emergency (usually drug of first choice), refractory congestive heart failure
- Pharmacological effects: relaxation of vascular smooth muscle by direct action of nitric oxide
- Clinical effects: vasodilation afterload and preload; can increase cardiac output in low output states, slight to no increase in heart rate
- Dosing: 0.1-0.3 $\mu\text{g}/\text{kg}/\text{min}$ increased by 0.1-0.3 $\mu\text{g}/\text{kg}/\text{min}$ every 5 minutes until response, then slow titration to every 15 minutes; maximum 10 $\mu\text{g}/\text{kg}/\text{min}$ (short term only); wean infusion slowly to prevent rebound hypertension
- Pharmacokinetics: $T_{1/2}$ 2 minutes, onset seconds, duration 10 minutes
- Contraindications: compensatory hypertension (i.e., AV shunting, coarctation of the aorta), inadequate cerebral circulation, congenital (Leber's) optic atrophy, tobacco amblyopia, use of sildenafil

- Side effects: hypotension, methemoglobinemia, headache, dizziness, restlessness, theoretical concern for coronary steal
- Caution: thiocyanate accumulates in renal dysfunction with infusions higher than $2\text{ }\mu\text{g/kg/min}$; try to limit use to less than 48 hours; toxicity can also occur with prolonged high-dose therapy; thiocyanide toxicity (levels of 5-10 mg/100 mL): altered mental status, abdominal pain, tinnitus, anorexia, and convulsions; monitor thiocyanate levels if prolonged infusion (>4 days) or if infusion rate greater than $4\text{ }\mu\text{g/kg/min}$; cyanide toxicity: cherry blood, almond breath, and metabolic or lactic acidosis; more common in patients with hepatic dysfunction

Norepinephrine (Levophed)

- Use/indications: acute hypotension, septic shock, neurogenic shock
- Pharmacological effects: predominantly alpha-adrenergic agonist; also some beta-1 agonist activity
- Clinical effects: constriction of resistance and capacitance vessels, leading to increased blood pressure and coronary artery blood flow; usually does not increase myocardial oxygen demand significantly
- Dosing: 8-12 $\mu\text{g/min}$; range 0.5-200 $\mu\text{g/min}$
- Pharmacokinetics: onset 1-2 minutes, duration 1-2 minutes
- Contraindications: hypovolemia, except as temporizing measure in emergency circumstances while awaiting volume repletion; peripheral or mesenteric vascular thrombosis, except in life-saving use
- Side effects: reduced blood flow to vital organs, decreased renal perfusion, tissue hypoxia, metabolic acidosis, arrhythmias, peripheral ischemia

Phenylephrine (Neo-Synephrine)

- Use/indications: hypotensive shock, paroxysmal supraventricular tachycardia

- Pharmacological effects: direct alpha-adrenergic agonist, constricts resistance and capacitance vessels
- Clinical effects: increased SVR, increased systolic and diastolic blood pressure, marked reflex bradycardia
- Dosing: hypotension: 50-300 $\mu\text{g}/\text{min}$; PSVT: rapid intravenous pressure not exceeding 500 μg , with subsequent doses determined by BP response
- Pharmacokinetics: onset immediate, duration 15-20 minutes
- Contraindications: severe hypertension, ventricular tachycardia
- Side effects: headache, hypertension, arrhythmia, tachycardia
- Comments: may get tachyphylaxis with continued use; bradycardia blocked by atropine

Vasopressin (Pitressin)—IV Use for Septic Shock and Gastrointestinal Hemorrhage

- Use/indications: unlabeled use for septic shock, unlabeled use for GI hemorrhage and esophageal varices; see ACLS guidelines for use with pulseless VT/VF
- Pharmacological effects: antidiuretic hormone
- Clinical effects: increases blood pressure, vasoconstriction, water permeability in renal tubule
- Dosing
 - For GI hemorrhage: 0.05 mU/kg/hr; double dosage as needed every 30 minutes (maximum 10 mU/kg/hr)
 - For septic shock: continuous infusion 0.04 U/min (constant infusion. no titration)
- Pharmacokinetics: $T_{1/2}$ 15-20 minutes
- Contraindications: hypersensitivity to vasopressin or any component of formulation; relative caution with patients with seizure disorder, migraine, vascular disease, coronary artery disease
- Side effects: increased blood pressure, arrhythmias,

venous thrombosis, vasoconstriction (at higher doses), chest pain, myocardial infarction

References

- ③ 1. Physician's Desk Reference. Thomson PDR, New Jersey, 2004.
- ② 2. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomized trial. *Lancet* 2000;356:2139-43.
- ③ 3. Girbes AR, Smit AJ. Use of dopamine in the ICU. *Clin Exp Hypertens* 1997;19:191-99.
- ③ 4. Debaveye YA, Van den Berghe GH. Is there still a place for dopamine in the modern intensive care unit? *Anesth Analg* 2004;98:461-68.

HYPERTENSIVE CRISES

Definition, Etiology, and Epidemiology^{1,2}

- Defined as uncontrolled arterial hypertension with resultant end-organ damage
 - End-organ damage can include encephalopathy, which comprises seizures, visual deficits, cerebrovascular accidents (CVA), myocardial ischemia/infarction, congestive heart failure (CHF) with pulmonary edema, aortic dissection, hemolytic anemia
 - Hypertensive urgency: systolic blood pressure (SBP) >210 or diastolic blood pressure (DBP) >120 without evidence of end-organ damage

Etiologies

- Uncontrolled essential hypertension
- Renal parenchymal diseases: acute and chronic renal failure
- Renal vascular diseases: bilateral renal artery stenosis
- Pregnancy-associated: eclampsia or pre-eclampsia
- Endocrine: pheochromocytoma, Cushing's syndrome, renin-secreting tumors or primary hyperaldosteronism (Conn's syndrome)

- Drugs: clonidine withdrawal, cocaine, sympathomimetics, erythropoietin, cyclosporine and other immunosuppressants, monoamine oxidase inhibitors
- Autonomic disorders: Shy-Drager syndrome, Guillain-Barré syndrome, acute intermittent porphyria, reflex autonomic dystrophy
- Neurological disorders as a physiological response to increased intracranial pressure (ICP): head injury, subarachnoid hemorrhage, brain tumor, CVA

Pathophysiology

- An event initiates a primary increase in intravascular resistance via norepinephrine and the renin-angiotensin-aldosterone axis
- Resultant pressure natriuresis and hypovolemia promote additional vasopressor activity
- The physiological vasodilatory response (via endothelial nitric oxide synthetase and prostacyclin activity) is inadequate, and uncompensated hypertension continues causing endothelial damage

Pearls of the History and Physical Examination

Symptoms

- Changes in vision, headache
- Confusion, seizures, neurological deficits
- Decreased urine output, uremic symptoms
- Abdominal pain, nausea, vomiting
- Chest pain (typical angina or radiation to back), shortness of breath, cough, dyspnea on exertion

Physical Examination

- Elevated SBP or DBP
- Papilledema or retinal hemorrhage, retinal exudates, retinal edema
- Examine pulses and blood pressures in all extremities to evaluate for dissection

- Bilateral crackles represent flash pulmonary edema from increased afterload or acute aortic insufficiency secondary to dissection
- Neurological examination to evaluate for focal deficits

Diagnostic Studies and Laboratory Values³

- Patients often require intra-arterial blood pressure monitoring
- Complete blood count with blood smear to evaluate for schistocytes (hypertension-associated microangiopathic hemolytic anemia)
- Electrolytes to assess renal function
- Urinalysis to evaluate for proteinuria, red blood cells/casts.
- Toxicology screen
- ECG may demonstrate left ventricular hypertrophy, myocardial ischemia
- Transthoracic echocardiogram to evaluate for diastolic dysfunction, impaired relaxation, valvular disease
- Chest x-ray to assess for pulmonary edema or widened mediastinum
- Other studies
 - Renovascular hypertension: captopril challenge test with serum renin levels before and after medication
 - Pheochromocytoma: spot metanephrine check (blood or urine) will capture unadulterated sample (before antihypertensive administration)
 - Primary aldosteronism: suspect with concomitant metabolic alkalosis, hypokalemia, low renin levels, and elevated aldosterone levels

Guide to Acute Management^{1,2}

- Goal: lower mean arterial pressure (MAP) by 20%-25% within 2 hours of onset and to 160/100 by 6 hours to allow cerebral vasculature to regain

autoregulatory function and prevent global hypoperfusion to brain

- Special situations:
 - Aortic dissection: more aggressive lowering of blood pressure (SBP to 110 mm Hg); use beta blockers and nitrates, i.e., nitroprusside (beta blockers prevent the reflex tachycardia that increases aortic shear stress and that can propagate dissection); labetalol is often a preferred agent with combined α - and β -receptor blocking properties
 - CVA: less aggressive lowering of blood pressure; patients may need higher arterial pressures to maintain cerebral vascular perfusion; avoid lowering MAP more than 20 mm Hg in first 24 hours
 - Hypertensive encephalopathy: consider anti-convulsants if seizures noted; avoid clonidine due to central nervous system (CNS) depressant effects; treat quickly before herniation ensues or CNS autoregulation fails completely
 - Pre-eclampsia: intravenous (IV) magnesium for seizure prophylaxis and hydralazine or labetalol; no angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as these can be teratogenic
 - CHF/acute coronary syndrome: nitroglycerin (NTG) or nitroprusside initially for preload reduction and/or coronary vasodilation
 - Cocaine-induced: labetalol (blocks alpha and beta receptors; therefore, no unopposed alpha stimulation by circulating cocaine metabolites); no clinical trials available to show benefit of this approach
 - Intensive care unit (ICU) monitoring (arterial line, reliable intravenous access, telemetry)
- Diuretics can be used during management of hypertensive emergency because sodium retention will increase as blood pressure is lowered; ensure patient is not volume-depleted.

PARENTERAL MEDICATIONS AVAILABLE

Medication	Dose	Onset/Peak/ Duration	Indications	Complications
Labetalol (alpha and beta blocker)	20-80 mg IV over 2 minutes, repeat q 15 min (maximum 300 mg), then start infusion 0.5-2.0 mg/min	O: 5 min P: 1-15 min D: 3-6 hr	Hypertension (HTN) emergency, pheochromocytoma clonidine withdrawal syndromes, cocaine use, aortic dissection	Bradycardia, heart block, bronchospasm, heart failure
Nitroprusside (arterio and venodilator)	0.1-0.3 µg/kg/min initially; can titrate rapidly in 10 µg/min increments at 5-min intervals; maximum infusion: 10 µg/kg/min	O: seconds P: 5 min D: 10 min	HTN emergency without renal insufficiency, heart failure, angina	Avoid use for >24 hr in renal insufficiency; increased risk of methemoglobinemia and thiocyanate toxicity: presents as altered mental status, abdominal pain, tinnitus, anorexia, convulsions (>5-10 mg/100 mL) Treat with 3% sodium nitrite
Esmolol (selective beta-1 blocker)	Loading dose 500 µg/kg over 1 min Maintenance 50-200 µg/kg/min; adjust in 25 µg/kg/min increments	O: immediate P: 5 min D: 10-30 min	HTN emergency: labetalol better choice; used predominantly during anesthesia	Bradycardia, heart block, hypotension, bronchospasm

(Continued on following page)

PARENTERAL MEDICATIONS AVAILABLE *(Continued)*

Medication	Dose	Onset/Peak/ Duration	Indications	Complications
Nicardipine (dihydropyridine calcium channel blocker)	5 mg/hr; titrate by 2.5 mg/hr every 5-15 min; maximum dose 15 mg/hr	O: 1 min P: 15 min D: 3 hr	HTN emergency, subarachnoid hemorrhage, similar to nitroprusside in efficacy	Avoid in aortic stenosis; flushing, headache, edema, rebound tachycardia
Hydralazine (arteriodilator)	10-40 mg IV	O: 5-15 min P: 10 min D: 2-6 hr	HTN emergency, especially in young or pregnant patients (those who can tolerate reflex tachycardia)	Reflex tachycardia; contraindicated in dissections; drug-induced lupus; headache angina; may contribute to increased ICP
Phentolamine (alpha blockers)	5-20 mg IV, repeat every 2-4 hr as needed	O: immediate D: 15-30 min	HTN emergency with pheochromocytoma or tyramine-associated catecholamine crisis	
Fenoldopam (peripheral dopamine receptor agonist)	0.1 $\mu\text{g/kg/min}$ and titrate in 0.05-0.1 $\mu\text{g/kg/min}$ increments at 15 min intervals; average dose 0.25-0.5 $\mu\text{g/kg/min}$	O: 10 min D: 1 hr	HTN emergency: increases renal perfusion	Headache, flushing, increased intraocular pressure; hypersensitivity to sulfites



Patient Care Warnings

- Admit to ICU, and monitor vital signs closely
- Parenteral medication choice depends on patient's medical problems, past and present
- Goal is to lower MAP by 20%-25% in first 6 hours
- Lower MAP more rapidly in aortic dissection and less rapidly in CVA
- Beware of arterial vasodilators that can cause reflex tachycardia

References

- ③ 1. Cherney D, Straus S. Management of patients with hypertensive urgencies and emergencies. *J Gen Intern Med* 2002;17: 938-45.
- ③ 2. Vaughn CJ, Delanty N. Hypertensive emergencies *Lancet* 2000;356:411-17.
- ③ 3. Kaplan NM *Clinical Hypertension*, 8th ed. Philadelphia, Lippincott Williams & Wilkins, 2002:339-56.

INTRACRANIAL HEMORRHAGE

Definition, Etiology, and Epidemiology¹

Intracerebral Hemorrhage

- Bleed involving small, penetrating arteries
- Hypertension is major cause, especially in deep parenchymal bleeds; other causes include cerebral angiod angiopathy, vasculitis, trauma, aneurysm, and arteriovenous malformation (AVM), which may lead to a more superficial bleed
- Lesions found in caudate, putamen, pons, cerebellum, peripheral cortex
- Third most common cause of cerebrovascular accident in United States

- Mortality rate is 35%-50% in 30 days
- Risk factors include hypertension, smoking, younger age

Subarachnoid Hemorrhage

- Rupture of saccular (berry) aneurysm or AVM²
- Occurs in fifth to sixth decade of life with equal gender distribution

Subdural Hematoma

- Tearing of bridging veins causes bleed into the potential space between the dura and arachnoid mater
- Acute or chronic presentations
- More common in elderly and alcoholic patients who have increased atrophy
- Trauma is usual etiology, and inciting event can be minor in severity

Epidural Hematoma

- Usually middle meningeal artery/vein tear bleed between dura and skull
- Most often related to blunt trauma; suspect skull fracture in such cases

Pearls of the History and Physical Examination³⁻⁵

- Obtain thorough and well-documented neurological examination at presentation (including Mini-Mental Status Exam, Glasgow Coma Scale, and fundoscopic examination)
- Ask about head trauma, recent or remote, in each of the following disease processes

Intracerebral Hemorrhage

- Sudden onset with progressing headache, nausea, and vomiting

- Evolving neurological deficits, change in consciousness
- Inquire about hypertension, trauma, time course of symptoms, bleeding diathesis, history of cocaine/amphetamine use, history of cancer and anticoagulant use

Subarachnoid Hemorrhage

- Inquire about onset and timing of headache: “worst headache of my life!”
- Evaluate retina for hemorrhage (clue to increased intracranial pressure [ICP])
- Raccoon eyes (periorbital ecchymoses), Battle’s sign (ecchymosis at mastoid process)
- History of adult polycystic kidney disease; coarctation of aorta, which is associated with berry aneurysms
- Focal neurological signs not universally present

Subdural Hematoma

- Acute or chronic presentation
- Acute: lethargic or comatose from moment of injury; typical complaint of headache and lateralizing symptoms
- Chronic: 20%-30% have no history of head trauma; headache; new onset or rapidly progressive dementia; new onset seizure activity
- Slow, progressive onset; possible symptoms of herniation

Epidural Hematoma

- Rapid decline in neurological function; typically trauma-related
- Brief loss of consciousness followed by lucid interval before decompensation into coma
- Progressive deterioration of mental status

Diagnostic Studies and Laboratory Values

- All patients require emergent, noncontrasted, head computed tomography (CT) with rapid interpretation to assess for presence and location of acute bleeding and evidence of midline shift and/or herniation
- Baseline complete blood count, electrolytes, coagulation studies, hepatic/renal laboratory tests, electrocardiogram.

Intracerebral Hemorrhage

- Head CT shows punctuated hemorrhage in deep bleeds and “lobar” hemorrhage in more superficial bleeds; possible extravasation into cerebrospinal fluid (CSF)

Subarachnoid Hemorrhage

- Xanthochromia in CSF within 6 hours of subarachnoid hemorrhage⁶
- Four-vessel angiography to evaluate anatomy (arteriovenous malformation, aneurysms, preoperative evaluation)
- Intracranial Doppler ultrasonography to evaluate vasospasm (if suspected)

Subdural Hematoma

- Head CT shows crescentic collection of blood in convex pattern
- If chronic subdural hematoma, noncontrasted CT will not show hematoma
- Contrasted CT will show fibrous cap around hematoma

Epidural Hematoma

- Head CT shows lenticular hematoma collection with biconcave appearance that does not cross suture lines

Guide to Acute Management

- Intensive care unit admission
- Early neurosurgery and neurology consult
- Airway and circulatory status management; avoid paralytic agents if possible so neurological examination is reliable
- Neurological checks every hour; invasive blood pressure monitoring
- Avoid antiplatelet and antithrombotic agents
- Correct any existing coagulopathy
- Monitor for complications, including elevated ICP, hydrocephalus, and herniation
- Ventriculostomy to relieve hydrocephalus and/or monitor ICP if indicated.
- Cerebral perfusion pressure (CPP) = mean arterial pressure (MAP) – ICP; goal CPP 60-70 mm Hg; American Heart Association guidelines recommend MAP <130 mm Hg and CPP >70 mm Hg for intracerebral hemorrhage
- Adjust MAP with labetalol, nitroprusside, dopamine, phenylephrine to manage CPP
- Suboccipital craniotomy for decompression of cerebellar hemorrhage (relieves obstructive hydrocephalus and prevents herniation)
- Steroids not indicated in intracerebral hemorrhage; remain controversial in subarachnoid hemorrhage
- Prophylactic antiseizure treatment controversial; no evidenced-based data
- Treat seizure activity as indicated; monitor for status epilepticus and treat aggressively

Intracerebral Hemorrhage

- Poor prognosis
- Bleed stops spontaneously in most cases
- Correct coagulopathy if present

- Primarily supportive care if no surgical indication planned

Subarachnoid Hemorrhage

- 30% survival in first 24 hours; improves within following week to 90%
- Neurosurgical clipping
- Endovascular coil placement within aneurysm by interventional neuroradiology
- Avoid rebleed by monitoring MAP and ICP aggressively
- Maneuvers to increase cerebral perfusion and prevent vasospasm
 - Hemodilution (modest effect)
 - Hypertension (induced with phenylephrine or dopamine)
 - Hypervolemia
- Nimodipine 60 mg po every 4-6 hr for 21 days to prevent vasospasm, which is a major cause of in-hospital mortality⁴
- Treat seizures prophylactically
- Hyponatremia: syndrome of inappropriate antidiuretic hormone secretion or cerebral salt wasting (see relevant renal sections for management guidelines)
- High in-patient mortality rate

Subdural Hematoma

- Surgical intervention with hematoma evacuation
- In chronic subdural hematoma, corticosteroids with or without resection indicated; may benefit from serial monitoring of hematoma size

Epidural Hematoma

- High mortality rate, but excellent prognosis if intervention occurs rapidly
- Emergent surgical intervention



Patient Care Warnings

- STAT noncontrast head CT
- Neurosurgical consultation
- Manage MAP aggressively to maintain stable CPP
- Anticipate complications such as herniation, hydrocephalus, and seizures
- Avoid paralytics for intubation

References

- ③ 1. Qureshi AI, Tuhim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1450-60.
- ③ 2. Schievink WI. Intracranial aneurysms. *N Engl J Med* 1997;336:28-40.
- ③ 3. Simon RP, Aminoff MJ, Greenberg DA. Headache and facial pain. *Clin Neurol* 1999; 77-101.
- ② 4. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm: A controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med* 1983;308:69-24.
- ③ 5. Ropper AH. Traumatic injuries to the head and spine. *Harrison's Principles of Internal Medicine*, 14th ed. New York, McGraw-Hill Publishing, 1998, 2390-98.
- ③ 6. Morgenstern LB, Luna-Gonzales H, Huber JC Jr, et al. Worst headache and subarachnoid hemorrhage: Prospective, modern computed tomography and spinal fluid analysis. *Ann Emerg Med* 1998;32:297-304.

STROKE

Definition, Etiology, and Epidemiology

- Stroke: disturbance in cerebral circulation causing acute onset of neurological deficit lasting >24 hours
- Transient ischemic attack (TIA): neurological deficit that resolves within 24 hours

- Reversible ischemic neurological deficit: neurological deficit that lasts more than 24 hours but resolves within 1 week (term now out of favor)
- Ischemic stroke (80%): impairment of cerebral perfusion by thrombotic or embolic event
- Hemorrhagic stroke (20%): cerebrovascular incompetence causing intracerebral, subarachnoid, subdural, or epidural hemorrhage; etiologies include arteriovenous malformations, aneurysms, lipohyalinosis, severe hypertension, trauma (see section titled Intracranial Hemorrhage for details).

ISCHEMIC ETIOLOGIES¹

Vascular Disorders	Cardiac Disorders	Hematological Disorders
Atherosclerosis	Atrial or ventricular thrombus	Thrombocytosis
Fibromuscular dysplasia	Rheumatic heart disease	Polycythemia
Vasculitis (systemic lupus erythematosus; polyarteritis nodosum; syphilitic, HIV, giant cell, or Takayasu's arteritis)	Dysrhythmias	Sickle cell disease
Dissection	Endocarditis	Leukostasis
Lacunar infarction	Mitral valve prolapse	Hypercoagulable states
Drug abuse	Prosthetic valves	
Migraine	Paradoxical emboli	
Cholesterol emboli	Atrial myxoma	

- Stroke is the third most common cause of death in the United States²
- Approximately 400,000 people are discharged from U.S. hospitals with stroke each year
- Prevalence of stroke: 794 per 100,000 persons

Pearls of the History and Physical Examination¹

- Early goals on initial evaluation:
 - Confirm whether neurological impairments are due to ischemia or hemorrhage
 - Quickly evaluate advisability of recombinant tissue plasminogen activator (rtPA) administration
 - Screen for acute medical or neurological complications of stroke (see below)
 - Collect historical/physical examination data to determine location of stroke
- Embolic strokes: sudden onset, previous TIAs in other distributions or multiple territories involved
- Thrombotic stroke: progression over minutes to hours, history of TIAs in same location
- Time of onset of first neurological symptom/sign is crucial (rtPA beneficial only if given within 3 hours of first sign/symptom); obtaining information using witnesses is crucial
- Obtain symptom complex of neurological deficit (i.e., mentation, presence of headache)
- Evaluate risk factors for atherosclerosis (hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, smoking, previous stroke, family history)
- Evaluate risk factors for embolic disease (dysrhythmias, recent myocardial infarction, left ventricular dysfunction, heart murmur/infective endocarditis)
- Consider nonischemic causes of focal neurological deficit: hypoglycemia, metabolic encephalopathies, medication-induced neurological compromise, post-ictal state, syncope, trauma, intracranial hemorrhage (subdural or epidural hematomas, intracerebral hemorrhage, or subarachnoid hemorrhage), malignancy and brain abscess
- Elucidate history to evaluate contraindications for rtPA administration²:
 - Head trauma or previous stroke in past 3 months

- Myocardial infarction in past 3 months
- Gastrointestinal or genitourinary hemorrhage in past 21 days
- Major surgery within 14 days
- Arterial puncture at a noncompressible site in past 7 days
- Lumbar puncture within past 7 days
- Any history of previous intracranial hemorrhage
- Blood pressure elevated (persistent systolic >185 mm Hg and diastolic >110 mm Hg)
- Evidence of active bleeding or acute trauma
- Oral anticoagulation with INR >1.5
- Elevated aPTT if on heparin in past 48 hours
- Platelet count less than 100,000 mm³
- Blood glucose <50 mg/dL
- Seizure with postictal residual neurological impairments
- Computed tomography (CT) revealing multilobar infarctions (hypodensity > one-third cerebral hemisphere)
- Physical examination: vital signs, neurological and cardiovascular examination crucial

NEUROLOGICAL PHYSICAL EXAMINATION PATTERNS^{1,3}

Left Hemisphere	Right Hemisphere	Subcortical	Brainstem
Aphasia	Left hemiparesis	Pure hemiparesis or sensory loss	Motor or sensory loss of all four limbs
Right hemiparesis	Left sensory loss	Dysarthria	Nystagmus
Right sensory loss	Left spatial neglect	Ataxic hemiparesis	Dysconjugate gaze
Right spatial neglect	Left homonymous hemianopia	No abnormalities of cognition, language, or vision	Crossed signs: ipsilateral face with contralateral limb

NEUROLOGICAL PHYSICAL EXAMINATION PATTERNS^{1,3} (Cont'd)

Left Hemi-sphere	Right Hemi-sphere	Subcortical	Brainstem
Right homonymous hemianopia	Poor left conjugate gaze		Pinpoint pupils (pons)
Poor right conjugate gaze	Urinary retention		Dysarthria
Urinary retention			Dysphagia
			Hyperthermia
			Ataxia

Diagnostic Studies and Laboratory Values⁴

- Emergent head CT without contrast; goal is door-to-CT interpretation within 45 minutes.
- Electrocardiogram with rhythm strip (findings with stroke include ST depression, QT prolongation, T-wave inversions, U waves)
- Glucose, complete blood count, serum electrolytes, PT/INR/aPTT, renal and liver function studies, arterial blood gas, toxicology screen, pregnancy test
- Check cerebrospinal fluid for red blood cells and xanthochromia if clinical suspicion high for subarachnoid hemorrhage and the head CT is without evidence of acute bleed

Guide to Acute Management^{2,3}

Ischemic Stroke

- Immediate evaluation and diagnosis to quickly rule out “mimickers” and exacerbating factors: hypoglycemia, seizures, syncope, tumors, hematomas

- Secure airway, and maintain circulatory status
- If rtPA candidate, admit to intensive care unit (ICU) or stroke unit; guidelines for rTPA use:
 - Infuse 0.9 mg/kg (maximum 90 mg) over 60 minutes, with 10% of dose given as bolus over 1 minute
 - Every 15 minutes, check neurology during infusion, every 30 minute for next 6 hours, then every hour for 24 hours
 - If severe headache, nausea, or vomiting, discontinue infusion and obtain STAT head CT to evaluate for hemorrhage
 - Every 15 minutes check blood pressure during infusion, every 30 minutes for next 6 hours, then every hour for 24 hours
 - Use antihypertensive agents (labetolol) if systolic blood pressure (SBP) >180 mm Hg and diastolic blood pressure (DBP) >105 mm Hg, but do not allow patient to become normotensive
 - Use labetalol in 10-mg intravenous (IV) infusion as needed or start infusion (2-8 mg/min)
 - Use nitroprusside infusion (0.5 mg/kg/min) if blood pressure not controlled with labetalol
- If not rtPA candidate, then administer aspirin 325 mg and monitor
- Admit patient to telemetry, stroke unit, or ICU
- Avoid central line, nasogastric tube, Foley catheter, and arterial lines if rtPA is a possibility
- Check vital signs every 30 minutes and neurological examination every hour
- Deep venous thrombosis prophylaxis with compression stockings
- Blood pressure control per guidelines: do not attempt to lower blood pressure acutely unless SBP >220 or DBP >120; treat with IV labetalol or nitroprusside if adequate control not achieved

- Avoid oral medications that do not allow for precise control; do not lower mean arterial pressure >20% unless severe end-organ damage (dissection, pulmonary edema, etc).
- Anticoagulation/antiplatelet agents as therapy for ischemic stroke:
 - Anticoagulation with unfractionated heparin, low molecular weight heparin, or other heparinoids not recommended
 - Anticoagulation within 24 hours of rTPA not recommended
 - Aspirin use within 24 hr of rTPA not recommended
- Consultations
 - Neurology: patient often best served on acute stroke service
 - Neurosurgery: with evidence of subdural or epidural hematoma, subarachnoid hemorrhage, hydrocephalus, cerebellar infarction or hemorrhage, intracerebral hemorrhage near peripheral neocortex
 - Interventional neuroradiology: intra-arterial thrombolysis, stenting
- Avoid hypotonic IV solutions, which may increase intracerebral edema
- Treat hyperthermia with antipyretics or cooling blankets (unproven benefit in outcomes)
- Evaluate for dysrhythmias as underlying cause of embolic event; optimize rate control for atrial tachyarrhythmias as needed, but avoid conversion to normal sinus rhythm in acute setting
- Consider transesophageal echocardiogram to evaluate intracardiac thrombus formation
- Neuroprotective agents such as nimodipine are not recommended in ischemic stroke
- Volume expanders and induced hypertension with vasoactive agents are not recommended

- Emergent carotid endarterectomy or external carotid-internal carotid bypass procedures are not recommended

Complications of Ischemic Stroke

- Elevated intracranial pressure (ICP)
 - Incidence peaks at 4-5 days
 - Fluid restriction
 - Elevate head of bed to approximately 30 degrees
 - Hyperventilate to decrease volume of intracranial blood and induce vasoconstriction (goal P_{CO_2} ~ 26-30 mm Hg); effect on ICP is short-lived
 - Consider mannitol 0.25-0.5 g/kg every 6 hours, with a maximum dose 2 g/kg/day to decrease cerebral tissue volume through diuresis
 - Intraventricular catheter placement if hydrocephalus appreciated by imaging
 - Ventriculostomy and craniotomy if evidence of cerebellar infarct causing compression in posterior fossa
- Seizure
 - Typically occurs within first 24 hours of cerebrovascular accident (CVA)
 - 4%-43% of ischemic CVA cases have seizure activity
 - No data to support seizure prophylaxis
 - Always treat status epilepticus
- Hemorrhagic conversion
 - Common complication of ischemic stroke
 - New or worsening neurological deficits after initial stroke should prompt emergent head CT to assess for conversion
 - Size and location determine further neurological deficits, complications
 - Anticoagulation, thrombolytic agents, and antiplatelet therapy can potentially increase the likelihood of serious hemorrhagic transformation⁴



Patient Care Warnings

- Always review contraindications for tPA before administration if patient is a candidate
- Do not lower blood pressure acutely to a normal level in the setting of stroke

References

- ③ 1. Simon RP, Aminoff MJ, Greenberg DA. Stroke. Clin Neurol 1999;279-304.
- ③ 2. Adams HP, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the stroke council of the American Stroke Association. Stroke 2003;34:1056-83.
- ③ 3. Adams HP, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale strongly predicts outcome after stroke. Neurology 1999;53:126-31.
- ③ 4. Brott T, Bogousslavsky J. Treatment for acute ischemic stroke. N Engl J Med 2000;343:710-22.

SEIZURES

Definition, Etiology, and Epidemiology¹

- Seizure: sudden change in behavior (motor function, sensory function, consciousness) that is the consequence of brain dysfunction
- Epilepsy: recurrent electrical hypersynchronization of neuronal networks in cerebral cortex¹
- Status epilepticus: continuous seizures lasting at least 5 minutes, or two or more discrete seizures between which there is incomplete recovery of consciousness

- Approximately 150,000 cases of status epilepticus occur yearly
- 20% overall annual mortality rate with status epilepticus¹
- Prolonged seizure activity causes cerebral damage through glutamate-mediated excitotoxicity
- Etiologies can be divided into epileptic seizures and nonepileptic seizures:
 - Epileptic seizure: 50% without identifiable cause; other causes include vascular disease, neoplasm, intracranial infection, congenital brain malformations, inborn errors of metabolism, trauma, fever, drug reaction, primary seizure disorder
 - Physiological nonepileptic seizures: hyperthyroidism, hyponatremia, sepsis, hypocalcemia, hypoglycemia, hypoxemia, porphyria, uremia, malignant hypertension, drug/toxin withdrawal or overdose
- With increasing age of patient, more seizures are caused by vascular disease, degenerative diseases, and neoplastic processes

Pearls of the History and Physical Examination

- Historical information is critical: locate witness who can relate time of onset, pattern of seizure activity, precipitating events (lighting, emotions); inquire about history of prior seizure, diabetes, stroke, medication list, medical history, drug use, trauma history, auras, jacksonian march, automatisms, tonic or atonic responses
- Conduct complete neurological examination; search for lateralizing signs that represent an intracranial process; focal neurological deficits may have limited utility for accurately predicting intracranial processes during the post-ictal state

Diagnostic Studies and Laboratory Values

- Capillary blood glucose, pulse oximetry/arterial blood gas (ABG), serum chemistries (particularly Na, Ca), renal function, liver function; anticipate a post-ictal leukocytosis with a left shift and metabolic acidosis
- Urine toxicology screen
- Consider porphyrin studies if porphyria suspected
- Serum antiepileptic drug concentrations (i.e., phenytoin, valproic acid)
- Electroencephalography (EEG) is necessary for monitoring during refractory status epilepticus, status epilepticus with unconsciousness, or in setting of paralytic use (patients on mechanical ventilation)
- Head computed tomography (CT) necessary on initial presentation of seizure to evaluate for gross abnormalities (hemorrhage, space-occupying lesions, stroke)
- Magnetic resonance imaging (MRI) is test of choice to assess for more subtle etiologies
- Lumbar puncture necessary if suspicion for infectious or metastatic etiologies after head CT performed

Guide to Acute Management²

- Monitor, support, and protect airway; ABG useful to evaluate severe hypoxemia or respiratory acidosis; metabolic acidosis purely from seizure rapidly normalizes but can induce hyperkalemia; start 100% oxygen and use oral or nasopharyngeal devices as needed to protect airway; if intubating, use short-acting paralytic such as vecuronium (0.1 mg/kg) as succinylcholine can also increase serum potassium
- Place patient into lateral decubitus position to prevent aspiration

- Check rapid glucose test; administer 1 amp D50% and intravenous (IV) thiamine 100 mg if indicated
- Monitor vital signs continuously; treat hyperthermia with cooling blankets/passive cooling
- Status epilepticus requires intensive care unit-level monitoring
- Neurology consultation
- Pharmacological therapy^{3,4}
 - Lorazepam (Ativan) 0.1 mg/kg IV at 2 mg/min; seizure may end as reversible causes corrected; if no change in seizure after 2-3 minutes, then consider:
 - Phenytoin (20 mg/kg IV at 50 mg/min) or fosphenytoin (20 mg/kg PE IV at 150 mg/min) (PE 5 phenytoin equivalent); monitor patient for hypotension, bradycardia, ectopy, phlebitis, and slow or stop infusion if complications arise; if no change in status after 20-25 minutes, then add 5-10 mg/kg more of phenytoin/fosphenytoin; after 30 minutes of seizure activity add: phenobarbital (20 mg/kg IV at 50-75 mg/min); potential complications include cardiovascular and respiratory collapse; escalated supportive therapy may include intubation, invasive blood pressure monitoring, vasoactive pharmacotherapy (dopamine, norepinephrine)
- Refractory status epilepticus requires:
 - Endotracheal intubation, continuous EEG monitoring, arterial and central venous catheter placement
 - Pharmacological therapy includes continuous infusions of midazolam (Versed): loading dose of 0.2 mg/kg, then 0.75-10 μ g/kg/min; or propofol: loading dose 1-2 mg/kg, then 2-10 mg/kg/hr
 - Continued maintenance doses of phenytoin or phenobarbital.
- Driving: Laws vary from state to state; see www.epilepsyfoundation.org for details regarding specific state laws.



Patient Care Warnings

- Status epilepticus requires intensive care unit monitoring
- Continuous EEG monitoring is underutilized yet necessary; request neurology input regarding its use and interpretation
- Consider early intubation and mechanical ventilation for patients in status epilepticus

References

- ③ 1. Chang BS, Lowenstein DH. Epilepsy. *N Engl J Med* 2003;349:1257-66.
- ③ 2. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med* 1998;338:970-76.
- ② 3. Leppik IE, Derivan AT, Homan RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983;249:1452-54.
- ② 4. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med* 1998;339:792-98.

ACUTE NEUROMUSCULAR DISORDERS

Myasthenia Gravis and Myasthenic Crisis

Definition, Etiology, and Epidemiology¹

- *My*: muscle; *asthenia*: weakness; *gravis*: severe
- Myasthenia gravis (MG) is neuromuscular disease process by which autoantibodies specifically bind to postsynaptic nicotinic acetylcholine receptors (AChR) and decrease their absolute concentration

- Results in impaired neuromuscular transmission and muscle weakness
- Classic example of type III immune-mediated response²
- The antibody-ChR complex causes dysfunction in three ways:
 - Direct inhibition of AChR
 - Sterically joining two AChRs, rendering them dysfunctional
 - Complement-mediated destruction of the postsynaptic end plate
- No underlying cause identified in 90% of patients
- Bimodal distribution

Characteristics	Early Onset	Late Onset
Age	Younger than 40 years	Older than 40 years
Gender	Female	Male
Thymic disease	Prominent	Rare
Anti-AchR Ab	Always present	Occasionally present

- Thymic disease (thymomas or hyperplasia) is the most notable known cause of MG
- Myasthenic crisis: an exacerbation of MG causing bulbar (swallowing, chewing) or respiratory muscle compromise
- Precipitating factors include infection, withdrawal from acetylcholinesterase inhibitors (pyridostigmine), and medications (e.g., beta blockers, calcium channel blockers, penicillamine, aminoglycosides, antimalarials)
- Differential diagnosis: Guillain-Barré syndrome (GBS), botulism, organophosphate toxicity, Eaton-Lambert syndrome, acetylcholinesterase inhibitor overdose, myopathic diseases

Pearls of the History and Physical Examination³

History

- Painless, fatigable weakness (acute, subacute, or relapsing/remitting)
- Diplopia, ptosis, shortness of breath, difficulty chewing or swallowing
- Proximal muscle weakness or weakness of small hand muscles.
- Investigate precipitating factors noted above

Physical Examination

- Proximal muscle weakness
- Inability to maintain upward gaze for 1 minute
- Unable to control secretions, drooling
- Tachypnea, dyspnea, nasal flaring, accessory muscle use
- Diminished reflexes
- Respiratory rate > 35/min (considered criterion for intubation)

Diagnostic Studies and Laboratory Values

- Tensilon test (edrophonium test): give intravenous (IV) 2-mg test dose administered over 15-30 seconds; 8 mg given 45 seconds later if no response is seen; test dose may be repeated after 30 minutes; monitor for improved upward gaze
- Send serum for autoantibody against AChR
- Arterial blood gas (ABG) is unreliable in neuromuscular respiratory failure as patients can compensate for hours with increased respiratory rate, although they can decompensate rapidly; waiting for evidence of hypercapneic respiratory failure will lead to delayed implementation of assisted ventilation

- Pulmonary function tests or bedside spirometry immediately; criteria for intubation include:
 - Forced vital capacity <15 mL/kg (<10 mL/kg correlates with respiratory failure)
 - Negative inspiratory pressure <20 cm H₂O
 - These are the same criteria for other progressive neuromuscular respiratory failures (GBS, botulism, etc.)

Guide to Acute Management⁴

- Assess quickly for signs of impending respiratory failure based on criteria above
- Investigate and treat underlying precipitating event
- MG patients receiving immunosuppressive agents are at risk for opportunistic infections
- Treat MG with acetylcholinesterase (AChEsterase) inhibitors (pyridostigmine)
- If unsure whether patient has crisis or cholinergic crisis secondary to AChEsterase inhibitor overdose, hold AChEsterase inhibitor and monitor
- Consider treatment with steroids, intravenous immunoglobulin (IVIG), and/or plasmapheresis in the setting of crisis



Patient Care Warnings

- Call neurology early in hospital course
- Intensive care unit monitoring for respiratory status, cardiac dysrhythmias
- Spirometry is a useful tool for assessing respiratory function and the need for mechanical ventilation

- Neurology consultation early
- Thymectomy when thymoma or thymic hyperplasia detected by computed tomography scan
- Extubation criteria are less well studied
- Differentiate between MG and botulism and GBS early
 - MG and botulism need endotracheal intubation to protect airway from secretions
 - GBS can at times be noninvasively ventilated initially

References

- ③ 1. Vincent A, Palace J, Hilton-Jones D. Myasthenia gravis. *Lancet* 2001;357:2112-28.
- ③ 2. Vincent A. Unraveling the pathogenesis of myasthenia gravis. *Nature Rev Immunol* 2002;2:797-804.
- ③ 3. Myasthenic gravis. In Goetz GG. *Textbook of Clinical Neurology*. WB Saunders, Philadelphia, 2nd ed, 2003:1118-20.
- ③ 4. Bedlack RS, Sanders DB. How to handle myasthenic crisis. *Postgrad Med* 2000;107: online.

Guillain-Barré Syndrome

Definition, Etiology, and Epidemiology¹

- Guillain-Barré syndrome (GBS) is a rapidly evolving symmetrical limb weakness with loss of tendon reflexes, absent or mild sensory signs, and variable autonomic dysfunction
- Reactive, self-limited, autoimmune disease caused by a previous viral or bacterial infection
- Antibodies (and cellular immune response) against offending agents display molecular mimicry with gangliosides on Schwann's cells, axonal cells, and motor end plates²
- *Campylobacter jejuni* is the most commonly associated bacterial infection

- Cytomegalovirus, Epstein-Barr virus, varicella zoster virus, and HIV have been associated with GBS.

Epidemiology

- 2.4 per 100,000 in United States in 1970-1980 developed GBS
- Most common among patients ages 20-40 years
- 33% require intensive care unit (ICU) monitoring with mechanical ventilation
- 5%-8% mortality rate despite aggressive ICU care
- 70% develop complete resolution of physical activity at 1 year

Time Course

- Onset of symptoms usually 11-14 days from exposure to viral/bacterial pathogen
- Nadir of symptoms 2 weeks from onset of symptoms

Pearls of the History and Physical Examination

- Ascertain history pertaining to recent viral or diarrheal illnesses

Diagnostic Criteria for Typical GBS

- Features required for diagnosis:
 - Progressive weakness in both arms and both legs
 - Areflexia
- Features strongly supporting diagnosis:
 - Progression of symptoms over days to 4 weeks
 - Relative symmetry of symptoms
 - Absent or minimal sensory symptoms or signs
 - Cranial nerve involvement, especially bilateral weakness of facial muscles
 - Recovery beginning 2-4 weeks after progression ceases

- Autonomic dysfunction as part of clinical syndrome
- Absence of fever at onset of symptoms
- High concentration of protein in cerebrospinal fluid, with fewer than $10 \times 10^3/\text{L}$ nucleated cells
- Typical electromyography or nerve conduction test (NCT) features (see following table)
- Features excluding diagnosis:
 - Confirmed alternative diagnosis of botulism, myasthenia, poliomyelitis, or toxic neuropathy
 - Abnormal porphyrin metabolism suggesting acute intermittent porphyria
 - Recent documented diphtheria infection
 - Clinical syndrome with purely sensory deficits without motor weakness

Diagnostic Studies and Laboratory Values

- Check antiganlioside antibodies

GBS Subtype	Pathology	Examination Findings	Testing	Facts
AIDP	Schwann's cells damaged	Flaccid paralysis	Slow NCT	Most common variant
AMSAN	Axonal degeneration	Motor and sensory paralysis	Slow or absent evoked responses	
AMAN	Pure motor axon degeneration	Ascending paralysis		Anti: C. jejuni anti-ganglioside Ab
MFS	Axons within brain stem affected	Ophthalmoplegia, areflexia, ataxia		Anti-Galb1-3GalNac Ab

AIDP: acute inflammatory demyelinating polyneuropathy; AMSAN: acute motor/sensory axon neuropathy; AMAN: acute motor axon neuropathy; MFS: Miller-Fisher syndrome; NCT: nerve conduction test

Guide to Acute Management^{3,4}

- Initiate supportive management measures
- See above for indications for intubation
- Low threshold for ICU transfer.
- Monitor airway, bulbar function, and circulatory parameters
- Prophylaxis for aspiration and venous thromboembolism
- IVIG (intravenous immunoglobulin) and plasma exchange have similar outcomes³
 - IVIG less expensive
 - Presumed mechanism of action: IVIG promotes blockade of FC receptors on macrophages, thereby preventing phagocytosis of opsonized cells; IVIG also neutralizes pathogenic auto-antibodies
 - Dose at $0.4 \text{ g/kg/d} \times 5 \text{ days}$ with infusion rate $0.5\text{--}4 \text{ mL/kg/hr}$
 - Complications: monitor for acute renal failure, thrombotic events, hemolytic anemia, and noncardiogenic pulmonary edema
 - Anaphylaxis is rare
 - Corticosteroids combined with IVIG have minimally improved outcomes within subset of patients⁵
- Steroids alone are ineffective



Patient Care Warnings

- IVIG or plasmapheresis necessary early in course of disease
- ICU monitoring necessary as a third of patients require mechanical ventilation

References

- ③ 1. Hahn AF. Guillain-Barré syndrome. *Lancet* 1998;352:635-41.
- ③ 2. Yuke N. Infectious origins of, and molecular mimicry in, Guillain-Barré and Fisher syndromes. *Lancet* 2001;1:29-37.
- ③ 3. Anonymous. Plasma exchange/sandoglobulin(R) Guillain-Barré syndrome trial group: Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. *Lancet* 1997;349:225-30.
- ① 4. Van Koningsveld R, Schmitz PIM, Meche A, et al. Effect of methylprednisolone when added to standard treatment with intravenous immunoglobulin for Guillain-Barré syndrome: Randomized trial. *Lancet* 2004;363:192-96.

CENTRAL VENOUS CATHETERS

Definitions/Indications

- To provide easy access to the central circulatory system for infusion of fluids, immediate resuscitation, nutritional support, monitoring of hemodynamics, pulmonary artery catheters, and temporary pacemakers
- Types of central venous catheters
 - Single lumen and multilumen
 - Impregnated with chlorhexidine, silver sulfadiazine and minocycline and rifampin; in some clinical trials, the use of these catheters has been shown to lower the rate of catheter-related bloodstream infection¹⁻³

Summary of Central Venous Catheters

Subclavian (SC) Line

- More comfortable for patient
- Often easier landmarks with obese patients
- Lower risk of catheter colonization compared with jugular or femoral³⁻⁶

- Difficult to compress with bleeding complications or inadvertent arterial puncture
- Increased risk for pneumothorax
- Lowest risk for catheter-related thrombosis^{3,4}

Internal Jugular (IJ) Line

- Lower risk for pneumothorax, but still present
- Compressible vessel to control bleeding
- Can be difficult in very obese patients and patients unable to lay flat (i.e., volume overloaded)
- Risk may be greater than with SC for thrombosis³
- Amenable for placement with ultrasound guidance³

Femoral (Fem) Line

- Less interference with cardiopulmonary resuscitation (CPR)/airway management and faster in CPR, although American Heart Association recommends using an SC or IJ when possible for enhanced drug delivery with less circulation time to the heart⁷
- Higher rate of catheter colonization in some reports⁴
- No risk of pneumothorax
- Increased risk of lower extremity deep venous thrombosis^{3,4,8}
- Caution in patients with inferior vena cava (IVC) filter as migration and entrapment of guidewire can occur⁹
- Increased risk for mechanical complications (arterial puncture, hematoma)

Note

- When using a pulmonary artery catheter and temporary pacemaker wire, two of the preferred sites for easier flow-directed placement include a right-sided IJ and a left-sided SC

Placement, Diagnostic Studies, and Laboratory Values

- Confirm normal coagulation studies and platelet count (and presence of IVC filter for femoral)
- Identify landmarks
- Preparations of line by flushing with normal saline
- Local anesthesia
- Trendelenburg's position for IJ and SC lines
- Proper sterile technique and cleaning for line placement
 - Proper hand-washing, aseptic technique, and barrier precautions recommended with sterile gloves, long-sleeved surgical gown, surgical mask with hair cover, and large sterile drapes^{3,10,11}
 - Cutaneous disinfection/swabbing of site with 2% chlorhexidine, 70% isopropyl alcohol, 10% or povidone iodine recommended; chlorhexidine may have best effect with a lower incidence of infection and bacteremia¹²
- Landmarks and technique
 - IJ: located at apex of triangle formed by the two heads of the sternocleidomastoid muscle and the clavicle; the IJ runs deep to the muscle and through the triangle; locate the carotid artery and then insertion should be lateral to the carotid pulsation; needle directed to ipsilateral nipple and angle of 20 degrees above the skin³
 - Approximate insertion length of line: right IJ: 14 cm; left IJ: 18 cm
 - SC: crosses under the clavicle just medial to the midclavicular point and an infraclavicular approach is taken 2-3 cm caudal to the midpoint of the clavicle; advance needle in direction of sternal notch until it touches against the clavicle and then pass beneath it in same direction³
 - Approximate depth of line: right SC: 12 cm; left SC: 16 cm

- Fem: palpate femoral arterial pulse and then insert needle aiming toward patient's head about 1 cm medial to the pulse at a point 1-3 cm below inguinal ligament
- Guidewire, dilation, line insertion to proper depth, then withdrawal and flush all ports
- With question of proper placement: if not obvious with darker color of venous blood, lack of pulsatile flow, and lower pressure, can confirm with blood gas or pressure transducer³
- Proper dressing on the insertion site and suturing
- Application of antibiotic ointment to catheter sites increases rate of colonization by fungi, causes antibiotic-resistant bacteria, has not been shown to lower rate of catheter-related bloodstream infection, and is not recommended^{3,13}
- Ultrasound guidance: real-time ultrasound guidance appears superior to blind landmark approach, especially during IJ line placement, with decreased risk of complications^{14,15}
- Prior to use: utility of chest x-ray¹⁶
 - Identify where catheter tip terminates and clear line for use
 - Evaluate and rule out pneumothorax or hemothorax
 - Not required after uncomplicated guidewire exchange in stable patients

Guide to Management

- Risk of infection is directly proportional to length of time the catheter is in place⁵
 - Routine scheduled changing of the central venous catheter by guidewire exchange or new puncture did not reduce the rate of catheter-related infections in some randomized trials, but risk of infection increases on fifth to seventh day^{3,17,18}

- Frequent routine clinical evaluation of regular central lines and sites of insertion is recommended along with replacement of dressings and hubs^{3,11}
- Removal recommended when central venous access no longer required
- Complications
 - Infections
 - Thrombus formation
 - Bleeding (especially with accidental arterial puncture)
 - Hematoma
 - Pneumothorax
 - Cardiac irritation and arrhythmia

Catheter-Related Infections

- 90% of nosocomial bloodstream infections are catheter-related¹⁹
- Signs/symptoms: examine frequently for: inflammation or purulence at the insertion site of catheter, fevers, chills, hypotension
 - Local catheter infections:
 - Catheter colonization
 - Phlebitis
 - Tunnel infection
 - Systemic catheter infections:
 - Bacteremia
 - Thrombophlebitis
 - Sepsis
 - Endocarditis
 - Abscess formation
- Diagnosis: rule out other sources: draw at least two sets of peripheral blood cultures to assess for systemic infection^{20,21}
 - Cultures can be drawn from the catheter port to confirm organism and for comparison and can be used to rule out line as source, given high negative predictive value^{3,22,23}

- Treatment: catheter should be removed if it is suspected source, and consider catheter tip culture.
- Vancomycin (for *Staphylococcus aureus* coverage) given initially in immunocompetent host along with other empiric therapy based on patient's other infection risks, length of time line has been in place, and microbiological environment of hospital
- Coverage for gram-negative should be added if immunocompromised or neutropenic; always consider fungal infections in intensive care unit settings and with use of parenteral nutrition³
- If only catheter-drawn blood culture is positive, and there is no clinical sign of infection, one may withhold treatment.¹⁹



Patient Care Warnings

- Always use caution with line placement, and watch for mechanical complications such as pneumothorax and bleeding/hematoma
- Use proper sterile technique, and clean area thoroughly
- Check coagulation studies and platelets prior to placement
- Always consider line as possible source of infection with proper symptoms
- Remove central lines when no longer needed

References

- ③ 1. Veenstra D, Saint S, Saha S, et al. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infections. A meta-analysis. JAMA 1999; 281:261.
- ③ 2. Raad I, Darouiche R, DuPuis J, et al. Central venous catheters

coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. *Ann Intern Med* 1997;127:267-74.

- ③ 3. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med* 2003;348:1123-33.
- ③ 4. Merrer J, Jonghe BD, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: A randomized controlled trial. *JAMA* 2001;286:700-707.
- ③ 5. Richet H, Hubert B, Nitemberg G, et al. Prospective multi-center study of vascular-catheter-related complications and risk factors for positive central-catheter cultures in intensive care unit patients. *J Clin Microbiol* 1990;28:2520.
- ③ 6. Collignon P, Soni N, Pearson I, et al. Sepsis associated with central vein catheters in critically ill patients. *Intensive Care Med* 1988;14:227.
- ③ 7. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: Advanced cardiovascular life support: Section 1: Introduction to ACLS 2000: Overview of recommended changes in ACLS from Guidelines 2000 conference. The American Heart Association in collaboration with the International Liaison Committee of Resuscitation. *Circulation* 2000;102:186.
- ③ 8. Durbec O, Viviani X, Potie F. Lower extremity deep venous thrombosis: A prospective, randomized, controlled trial in comatose or sedated patients undergoing femoral vein catheterization. *Crit Care Med* 1997;25:1982.
- ③ 9. Duong MH, Jensen WA, Kirsch CM, et al. An unusual complication during central venous catheter placement. *J Clin Anesth* 2001;13:131.
- ③ 10. O'Grady NP, Gerberding JL, Weinstein RA, et al. Patient safety and the science of prevention: The time for implementing the guidelines for the prevention of intravascular catheter-related infections is now. *Crit Care Med* 2003;31:291.
- ③ 11. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;132:391.
- ③ 12. Maki DG, Ringer M, Alvarado CJ. Prospective randomized trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991;338:339.
- ③ 13. Pearson ML. Guideline for prevention of intravascular device-related infections. *Infect Control Hosp Epidemiol* 1996;17:438-73.
- ③ 14. Hind D, Calvert N, McWilliams R, et al. Ultrasound locating devices for central venous cannulation: A meta-analysis. *Br Med J* 2003;327:361.
- ③ 15. Gordon AC, Saliken JC, Johns D, et al. US-guided puncture of the internal jugular vein: Complications and anatomic considerations. *J Vasc Interv Radiol* 1998;9:333.
- ③ 16. Frassinelli P, Pasquale MD, Cipolle MD, et al. Utility of chest

- radiographs after guidewire exchanges of central venous catheter. *Crit Care Med* 1998;26:611.
- ③ 17. Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med* 1992;327:1062.
 - ③ 18. Eyer S, Brummitt C, Crossley K, et al. Catheter-related sepsis: Prospective, randomized study of three methods of long-term catheter maintenance. *Crit Care Med* 1990;18:1073.
 - ③ 19. Maki DG. Infections due to infusion therapy. In Bennett JV, Brachman PS (eds), *Hospital Infections*, 3rd ed. Boston, Little, Brown, 1992.
 - ③ 20. Bryant JK, Strand CL. Reliability of blood cultures collected from intravascular catheter versus venipuncture. *Am J Clin Pathol* 1987;88:113.
 - ③ 21. Everts RJ, Vinson EN, Adholla PO, et al. Contamination of catheter-drawn blood cultures. *J Clin Microbiol* 2001;39:3393.
 - ③ 22. Wormser GP, Onorato IM, Preminger TJ, et al. Sensitivity and specificity of blood cultures obtained through intravascular catheters. *Crit Care Med* 1990;18:152.
 - ③ 23. Tafuro P, Colbourn D, Gurevich I, et al. Comparison of blood cultures obtained simultaneously by venipuncture and from vascular lines. *J Hosp Infect* 1986;7:283.

FEVER AND LEUKOCYTOSIS IN THE ICU

Definition, Etiology, and Epidemiology

- Fever is defined as $>38.3^{\circ}\text{C}$ ^{1,2}
- In the absence of fever: unexplained hypotension, tachycardia, tachypnea, confusion, rigors, skin lesions, oliguria, lactic acidosis, leukocytosis, leukopenia, thrombocytosis, or thrombocytopenia may warrant infectious work-up^{2,3}
- Diagnostic dilemma is to exclude noninfectious causes and then determine the infected site¹

Pearls of the History and Physical Examination

- Localizing obvious source requires focused diagnostic work-up¹
- Evaluation for noninfectious causes: see below¹

- Wound infection: consider in all postoperative patients with fever and inspect for evidence of infection, with exploration if necessary¹
- Fever patterns do not provide reliable and consistent diagnostic clues^{1,3}
 - Temperature $>41^{\circ}\text{C}$ more likely due to central nervous system (CNS) processes (hemorrhage, trauma, infection, malignancy), infusion-related sepsis (contaminated infusate), malignant hyperthermia, bacterial infection (rare), drug fever (usually 39° - 41°C), or neuroleptic malignant syndrome^{1,3,4}
 - Noninfectious causes usually do not lead to fever greater than 38.9° - 41°C , and such temperatures should be considered to be secondary to infectious causes¹
 - Persistent fever despite appropriate empiric antibiotics suggests an unidentified fungal infection¹
 - Postoperative fever in first 48 hours is usually noninfectious (72%), but more likely to be infectious after 48 hours²

Diagnostic Studies and Laboratory Values for Patients With Fever

- Blood cultures are indicated in all febrile patients due to excess morbidity and mortality rates associated with bacteremia¹
- Sputum culture and chest x-ray for patients on mechanical ventilation
- Stool study for *Clostridium difficile* toxin and fecal leukocytes if loose stools are present¹
- Consider computed tomography (CT) of sinuses if nasal tubes present¹
- Urinalysis and culture if structurally abnormal urinary tract or following urinary tract manipulations including Foley catheterization¹
- CT of abdomen for patients with abdominal signs

(tenderness, distention, inability to tolerate enteral feeds), recent abdominal surgery, or prolonged fever after abdominal surgery^{1,3}

- Ultrasound of right upper quadrant if localized tenderness is present¹
- If no obvious source of fever: remove all central lines more than 48 hours old, and obtain semiquantitative or quantitative culture of tips¹

Guide to Acute Management

- In absence of clinically obvious source of infection, drawing blood cultures followed by clinical observation may be appropriate in the stable patient¹
 - Exceptions include all neutropenic patients, and any patient with signs of sepsis or fever greater than 39°C¹
- Persistent fever after 48 hours or progressive signs of infection requires more intensive work-up for potential infectious causes¹
- Antipyretic therapy: treat fever from acute brain insults, patients with limited cardiopulmonary reserve, and if temperature is greater than 40°C^{1,3}
- Hypothermic blankets are no more effective than antipyretics and may be associated with large temperature fluctuations and further increases in oxygen consumption¹

Causes of Fevers in the Intensive Care Unit (ICU)

Noninfectious Fevers

- Most are usually obvious¹
- Most common noninfectious causes: acute myocardial infarction, pulmonary embolus, pulmonary infarction, acute pancreatitis, gastrointestinal hemorrhage, phlebitis, hematomas, acute gout attacks,

fever from malignancy, and drug hypersensitivity⁴
(for more extensive list, see reference 1)

- Drug fever
 - Consider in patients with otherwise unexplained fever, particularly if on beta-lactam antibiotics, antiarrhythmics (especially procainamide or quinidine), antiseizure medicine (especially phenytoin), sulfa-containing drugs (furosemide, some stool softeners, sulfonamide antibiotics), amphotericin B, methyl dopa¹⁻³
 - Leukocytosis with left shift is often present; eosinophilia (<20%) and rash (5%-10%) are uncommon¹⁻³
- Atelectasis
- Blood transfusions
 - Febrile reactions complicate 0.5% of blood transfusions 30 min to 2 hours after transfusion begins and last 2–24 hours^{1,2}
- Deep venous thrombosis
 - Routine venography should not be done as part of the initial work-up of fever unless other signs or symptoms suggest this diagnosis as predictive value is poor¹
- Acalculous cholecystitis
 - Frequently unrecognized and potentially life-threatening illness (1.5% of critically ill patients)¹
 - Diagnosis should be considered in every critically ill patient who has clinical findings of systemic inflammatory response syndrome without obvious source¹
 - Right upper quadrant pain is suggestive but often absent^{1,5,6}
 - Diagnostic studies and laboratory values
 - Ultrasound (US): most commonly used diagnostic test to assess for increased wall thickness^{1,7,8}
 - Hepatobiliary scintigraphy has a false-positive rate >50% in critically ill patients, but a normal scan virtually excludes the diagnosis^{1,9}

- CT scanning reported to have high sensitivity and specificity but no prospective studies comparing with US¹
- Guide to acute management¹
 - Percutaneous cholecystostomy is usually procedure of choice^{1,10}
 - Open cholecystectomy is recommended should abdominal signs, fever, and leukocytosis not improve within 48 hours of percutaneous cholecystostomy¹
 - Antibiotics to cover biliary pathogens, notably *Escherichia coli*, *Klebsiella*, and *Enterococcus faecalis* are an adjunctive therapy⁶

Infectious Fevers

- Ventilator-associated pneumonia (VAP)
 - 25% of ventilated patients¹
 - Attributed mortality rate at least 27%^{1,11}
 - Diagnostic studies and laboratory values
 - Leukocytosis or leukopenia^{1,12}
 - New or worsening infiltrate on chest x-ray³
 - Clinical criteria alone are unreliable in the diagnosis^{1,3}
 - Invasive and semi-invasive (mini-bronchoalveolar lavage) can be used to confirm diagnosis, identify the pathogen, and narrow antibiotic coverage^{3,13,14}
 - Guide to acute management
 - Early initiation (when VAP first suspected) of broad-spectrum antimicrobial coverage targeted at mRSA and gram-negative rod (including *Pseudomonas aeruginosa*) improves outcomes^{1,12,14,15}
- Sinusitis
 - 5% of nosocomial infections in the ICU³
 - Occur in up to 85% of patients after 1 week of nasotracheal intubation¹; predisposing conditions: nasotracheal tubes, nasal packing, nasogastric tubes, facial fractures, steroid use^{3,16}
 - Radiological evidence of sinusitis occurs more frequently with nasal versus oral tubes (96% versus 23%)¹⁶

- Fever and leukocytosis often present but purulent drainage typically absent³
- Diagnostic studies and laboratory values
 - CT scan showing total opacification or an air-fluid level within any of the paranasal sinuses is sensitive but not specific (38%)^{1,2,16}
 - Confirm with puncture; drainage and Gram's stain/culture of fluid from involved sinus²
 - Approximately 50% of isolated organisms are gram-negative bacteria¹⁶
- Guide to acute management
 - Removal of all nasal tubes, drainage of involved maxillary sinuses, and broad spectrum antibiotics are recommended^{1,2}
- Catheter-associated sepsis (see separate section on this topic)
 - Central venous lines may be source of fever despite only 50% showing signs of infection at site of catheter insertion⁴
 - Radial artery catheters are rarely associated with sepsis, and when this occurs it is usually apparent by clinical examination⁴
- Urinary tract infections
 - True incidence in ICU unclear due to lack of criteria differentiating asymptomatic bacteriuria from symptomatic infection^{1,2,3}
 - Less than 3% of hospitalized patients with catheter-associated bacteriuria become bacteremic¹⁷
 - Urosepsis rarely develops de novo in the ICU except in nonleukopenic immune-compromised hosts (diabetics, lupus, steroid use), patients with preexisting renal disease, or partial or total obstruction of the urinary tract⁴
 - Guide to acute management
 - Data for treating hospitalized patients with bacteriuria stem from a single study showing a 2.8-fold increase in mortality rate when bacteriuria was present; results

may not apply to current practice according to some expert opinion^{1,18}

- Treat bacteriuria following genitourinary manipulation, kidney stones, or urinary obstruction¹
- *C. difficile* colitis
 - Up to 20% of hospitalized patients become infected with *C. difficile*^{1,19}
 - Four basic presentations
 - Asymptomatic carrier state: two-thirds of cases^{1,19,20}
 - Antibiotic-associated diarrhea: mild-to-moderate diarrhea, occasional lower abdominal cramping, and no systemic symptoms^{1,19}
 - Colitis without pseudomembranes: profuse diarrhea, abdominal pain, distention, low-grade fever, nausea, anorexia, malaise, leukocytosis, increased fecal leukocytes^{1,19,20}
 - Pseudomembranous colitis: marked abdominal and systemic signs of illness; can develop fulminant colitis (3% of total cases), leading to perforation, prolonged ileus, megacolon, and death^{1,20}
 - Pearls of the history and physical examination
 - Fever and diarrhea with recent antibiotic or chemotherapeutic agent; especially cephalosporins, clindamycin, ampicillin²
 - Rare patients may present with ileus or toxic megacolon without diarrhea, especially postoperative patients^{2,20}
 - Diagnostic studies and laboratory values
 - Leukocytosis may be present
 - Tissue culture is the gold standard (sensitivity 94%-100%, specificity 99%) but rarely performed due to cost and time¹
 - ELISA toxin assay: current diagnostic test of choice with sensitivity 70%-90%, specificity 99%^{1,2,19-22}
 - Two to three stool specimens for fecal leukocytes and *C. difficile* (C diff) toxin are recommended to increase yield^{2,21}
 - Guide to acute management

- No treatment for asymptomatic carrier state: treatment does not decrease carrier state^{19,20}
- Treat more severe diarrhea or milder colitis with oral metronidazole as first-line agent^{19,20}
- Oral vancomycin is second-line therapy due to cost and resistance concerns (vancomycin-resistant enterococci)^{19,20}; use when intolerant to or failure to respond to metronidazole²⁰
- Severe or fulminant colitis: oral vancomycin is recommended as first-line therapy²⁰
- If ileus is present: use intravenous (IV) metronidazole
- Supplement IV metronidazole with vancomycin by nasogastric tube or enema in critically ill patients
- Consider empiric therapy while workup in progress with severe disease²
- Surgical intervention (laparotomy and colectomy) may be lifesaving in patients with impending or actual perforation^{19,20}
- Candidal infections
 - 17% of nosocomial ICU infections are caused by fungi¹
 - Diagnosis often made clinically and confirmed by histopathological evidence of candidal invasion of deep tissue²³
 - Major risk factors: more than two antibiotics, colonization at more than two sites, gastrointestinal surgery, intra-abdominal abscess, systemic steroids, total parenteral nutrition, diabetes mellitus, chronically immunosuppressed state²³
 - Fundoscopic examination for evidence of endophthalmitis²⁴
 - Diagnostic studies and laboratory values
 - Blood cultures positive in about 50% of disseminated candidiasis²³
 - Isolation from pulmonary samples usually reflects colonization as candida pneumonia exceedingly rare
 - *Candida* in catheterized urine usually represents col-

onization; candidemia from candiduria extremely rare^{1,25-27}

- Isolation of *Candida* from more than two different body sites is useful predictor of disseminated disease²³
- Guide to acute management
 - Consider empiric treatment after cultures drawn if patient has two major risk factors, isolation of *Candida* from two or more sites, and persistent fever despite appropriate antibiotic coverage^{23,24,27}
 - Treatment agent depends on strain of *Candida* and site/type of infection
 - Studies have shown therapeutic equivalence of (caspofungin and fluconazole) to amphotericin B in immunocompetent patients with less drug toxicity^{26,28-31}
 - *Candida glabrata* and *Candida krusei* are sometimes fluconazole-resistant, and caspofungin or amphotericin B is recommended²⁷
 - Treat candiduria if symptoms present, neutropenia, renal allograft present, or pre- /posturinary tract manipulations^{24,27}
 - Otherwise treatment not necessary, but remove urinary catheters if possible^{24,27}
- Nosocomial meningitis: very rare in ICU except following neurosurgical procedures¹
- Lumbar puncture indicated for workup of fever in ICU only if patient has meningeal signs, contiguous infection, recent neurosurgical procedure,¹ or presence of ventriculostomy catheter or ventriculoperitoneal (VP) shunt²
- In patient with VP shunt who develops stupor or signs of meningitis, the catheter should be removed and the tip cultured²

References

1. Marik PE. Fever in the ICU. *Chest* 2000;117:55-69.
2. O'Grady NP, Barie PS, Bartlett J, et al. Practice parameters for evaluating new fever in critically ill adult patients. *Crit Care Med* 1998;26:392-408.

3. Cunha BA, Shea KW. Fever in the intensive care unit. *Infect Dis Clin North Am* 1996;10:185-209.
4. Cunha BA. Fever in the critical care unit. *Crit Care Clin* 1998;14:1-14.
5. Orlandon R, Gleason E, Drezner AD. Acute acalculous cholecystitis in the critically ill patient. *Am J Surg* 1983;145:472-76.
6. Barie PS, Fischer E. Acute acalculous cholecystitis. *J Am Coll Surg* 1995;180:232-43.
7. Deitch EA, Engel JM. Acute acalculous cholecystitis, ultrasonic diagnosis. *Am J Surg* 1981;142:290-92.
8. Deitch EA. Utility and accuracy of ultrasonically measured gallbladder wall as a diagnostic criterion in biliary tract disease. *Dig Dis Sci* 1981;26:686-93.
9. Kalff V, Froelich JQ, Lloyd R, et al. Predictive value of abnormal hepatobiliary scan in patients with severe intercurrent illness. *Radiology* 1983;146:191-94.
10. van Overhagen H, Meyers H, Tilanus HW. Percutaneous cholecystostomy for patients with acute cholecystitis and increased surgical risk. *Cardiovasc Intervent Radiol* 1996;19:72-76.
11. Fagon JY, Chastre J, Hance A, et al. Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993;94:281-88.
12. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on therapy and outcome of ventilator-associated pneumonia. *Chest* 1997;111:676-85.
13. Sterling TR, Ho EJ, Brehm WT, et al. Diagnosis and treatment of ventilator-associated pneumonia: Impact on survival, a decision analysis. *Chest* 1998;110:1025-34.
14. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: Implications for the antibiotic management of ventilator-associated pneumonia. *Chest* 1998;113:412-20.
15. Rello J, Gallego M, Mariscal D, et al. The value of routine microbial investigation in ventilator associated pneumonia. *Am J Respir Crit Care Med* 1997;156:196-200.
16. Rouby JJ, Laurent P, Gosnach M, et al. Risk factor and clinical relevance of nosocomial maxillary sinusitis in the critically ill. *Am J Crit Care Med* 1994;150:776-83.
17. Kreiger JN, Kaiser DL. Urinary tract etiology of bloodstream infections in hospitalized patients. *J Infect Dis* 1983;148:57-62.
18. Platt R, Polk BF, Murdock B, et al. Mortality associated with nosocomial urinary-tract infections. *New Engl J Med* 1992;307:637-42.
19. Kelly CP, Pothoulakis C, LaMont JT. Clostridium difficile colitis. *New Engl J Med* 1994;330:257-62.
20. Kelly CP, LaMont JT. Clostridium difficile infection. *Ann Rev Med* 1998;49:375-90.
21. Manabe YC, Vinetz JM, Moore RD, et al. Clostridium difficile colitis: An efficient clinical approach to diagnosis. *Ann Intern Med* 1995;123:835-40.

22. Brazier JS. The diagnosis of clostridium difficile-associated disease. *J Antimicrob Chemother* 1998;41:Supp C,29-40.
23. Midha NK, Stratton CW. Laboratory tests in critical care. *Crit Care Clin* 1998;14:15-34.
24. Pappas PG, Rex JH, Sobel JD, et al. IDSA guidelines: Guidelines for the treatment of candidiasis. *Clin Infect Dis* 2004;38:161-89.
25. Nolla-Salas J, Sitges-Serra A, Leon-Gil C, et al. Candidemia in non-neutropenic critically ill patients: Analysis of prognostic factors and assessment of systemic antifungal therapy. *Intensive Care Med* 1997;23:23-30.
26. Phillips P, Shafran S, Garber G, et al. Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. *Eur J Clin Microbiol Infect Dis* 1997;16:337-45.
27. Edwards JE, Bodey GP, Bowden RA, et al. International conference for the development of a consensus on the management and prevention of severe candidal infections. *Clin Infect Dis* 1997;25:43-59.
28. Mora-Duarte J, Bett R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *New Engl J Med* 2002;347:2020-29.
29. Abele-Horn M, Kopp A, Sternberg U, et al. A randomized study comparing fluconazole with amphotericin B/5-flucytosine for the treatment of systemic candida infections in intensive care patients. *Infection* 1996;24:426-32.
30. Anaissie EJ, Darouiche RO, Abi-Said D, et al. Management of invasive candidal infections: Results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. *Clin Infect Dis* 1996;23:964-72.
31. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *New Engl J Med* 1994;331:1325-30.

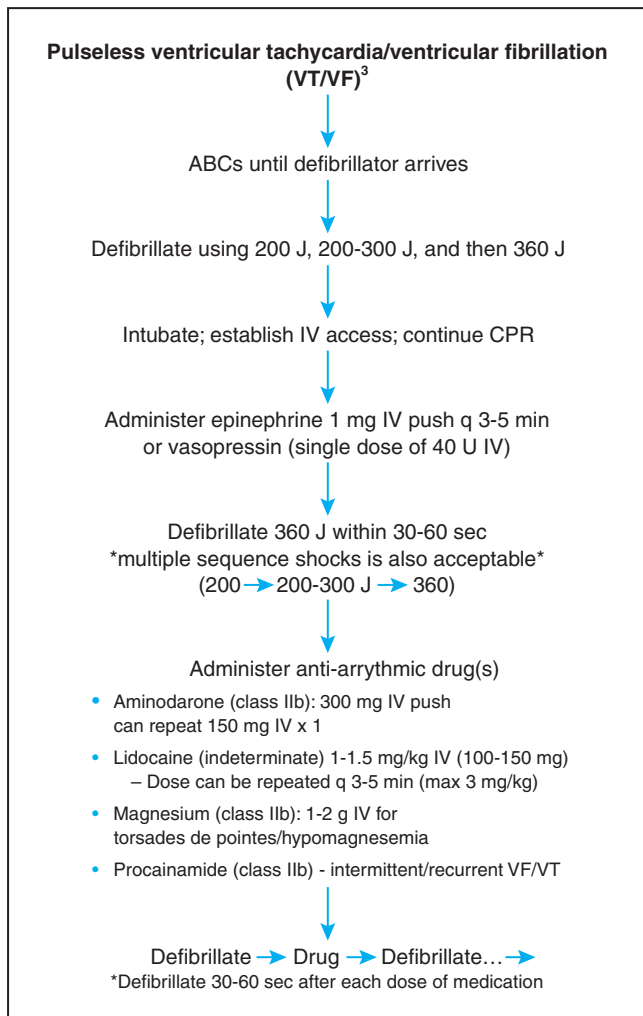
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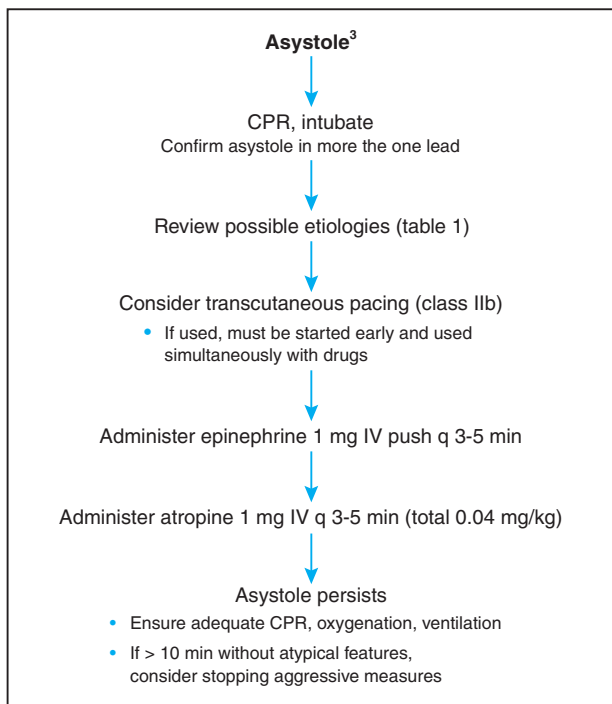
Predictors of Successful Resuscitation^{1,2}

- Patient has a witnessed arrest
- Initial cardiac rhythm is ventricular tachycardia/ventricular fibrillation
- Regained pulse during first 10 minutes of cardiopulmonary resuscitation (CPR)
- Absence of the need for endotracheal intubation

Guide to Acute Management

- ABCs: airway, breathing, circulation
- Levels of evidence per American Heart Association guidelines in parentheses





PEA³

- Pulseless electrical activity (PEA) = Electromechanical dissociation (EMD)
- Idioventricular rhythms
- Pseudo-EMD
- Ventricular escape rhythms
- Postdefibrillation idioventricular rhythms
- Bradysystolic rhythms



Review possible etiologies (table 1)



Intubate; establish IV access; continue CPR



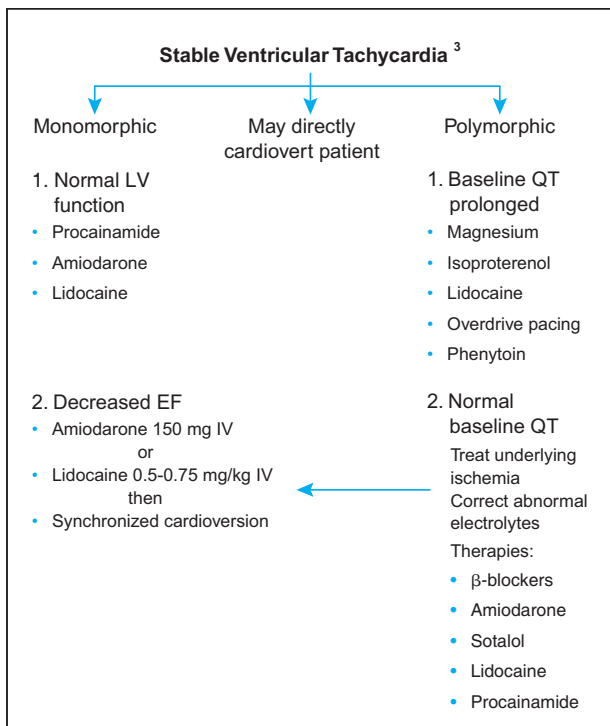
Administer epinephrine 1 mg IV push q 3-5 min



Atropine 1 mg IV (if PEA is <60 bpm/relative bradycardia)
Repeat q 3-5 min (total 0.04 mg/kg)

Role of HCO_3^- (1 mg/kg):

- Class I indication for hyperkalemia
- Class IIa: preexisting HCO_3^- responsive acidosis, TCA overdose, alkalinize urine
- Class IIb: prolonged cardiac arrest period
- Class III (not indicated): hypoxic lactic acidosis, hypercapneic respiratory acidosis



TREATABLE CONDITIONS ASSOCIATED WITH CARDIAC ARREST (5Hs AND 5Ts)²

Condition	Clinical Circumstance	Therapy
Hypovolemia/ hemorrhage, anemia	Major burns, diabetes, GI loss, pregnancy, shock, trauma	• Intravenous fluids • Packed red blood cells • Localize blood loss
Hypoxia	Presume in all patients with cardiac arrest	• Ensure adequate CPR • Ensure oxygenation/ventilation/correct endotracheal tube (ETT) placement

TREATABLE CONDITIONS ASSOCIATED WITH CARDIAC ARREST (5Hs AND 5Ts)² (Continued)

Condition	Clinical Circumstance	Therapy
Hydrogen ion (acidosis)	Diarrhea, drugs/toxins, prolonged resuscitation, renal failure, shock/sepsis	• Ensure adequate CPR • Ensure oxygenation/ventilation/correct ETT placement • HCO_3
Hyperkalemia Hypokalemia Hypomagnesemia	Hyperkalemia: renal failure, hemodialysis patients, metabolic acidosis, hemolysis, rhabdomyolysis, significant tissue injury Hypokalemia: alcohol use, diabetes, diuretics, gastrointestinal losses, hypomagnesemia Hypomagnesemia: alcohol (EtOH) use, burns, diabetic ketoacidosis, diuretics, drugs, diarrhea	Hyperkalemia: • 10% calcium chloride (do not give if due to digoxin toxicity) • 10 U reg insulin with D_{50} intravenous (IV) • 1-2 amps HCO_3 (class I) • Albuterol nebulizers Hypokalemia: • 2.5 with cardiac arrest → 2 mEq/min IV up to 10-15 mEq Hypomagnesemia : • 1-2 g MgSO_4 over 2 min
Hypothermia	EtOH abuse, burns, central nervous system process, elderly/debilitated, near-drowning, exposure, trauma, endocrine disease	• If severe ($T < 30^\circ\text{C}$), limit shocks for ventricular tachycardia/fibrillation to 3 attempts • Initiate internal rewarming • Hold further resuscitation/shocks until $T > 30^\circ\text{C}$ • If $T 30^\circ\text{-}34^\circ\text{C}$ proceed with resuscitation

(Continued on following page)

TREATABLE CONDITIONS ASSOCIATED WITH CARDIAC ARREST (5Hs AND 5Ts)² (Continued)

Condition	Clinical Circumstance	Therapy
Toxins/tablets	EtOH abuse, bizarre behavior, psychological history, toxicology syndrome, occupation or industrial exposure	• Urine toxicology screen • Consult toxicologist as needed • Treat suspected ingestion (charcoal/lavage) • Prolonged resuscitation may be appropriate
Tamponade	Cancer, pericarditis, trauma, post-cardiac surgery, status post myocardial infarction, hemorrhagic diathesis	• IV fluids • Bedside transthoracic echocardiogram • Pericardiocentesis: needle in subxiphoid space at 45° toward left shoulder
Tension pneumothorax	Central line placement, mechanical ventilation, pulmonary disease, thoracentesis, trauma	• Needle decompression: insertion of 14 gauge angiocatheter into second intercostal space, midclavicular line on side of pneumothorax, followed by chest tube placement
Thrombosis, coronary	Consider in all patients, especially with preexisting history of or risk factors for coronary artery disease	• Emergent percutaneous coronary intervention/coronary artery bypass grafting • Consider thrombolytics • Inotropic support/intra-aortic balloon pump as needed
Thrombosis, pulmonary	Hospitalized patient, recent surgical procedure, peripartum, history of deep venous thrombosis	• IV fluids • Vasopressor therapy as needed • Consider thrombolytics, percutaneous interventional techniques, surgical intervention

References

- ② 1. Van Walraven C, Forster AJ, Parish DC, et al. Validation of a clinical decision aid to discontinue in-hospital cardiac arrest resuscitation. *JAMA* 2001;285:1602-06.
- ③ 2. Eisenberg MS, Mengert TJ. Cardiac resuscitation. *New Engl J Med* 2001;344:1304-13.
- ③ 3. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: Part 6: Advanced cardiovascular life support: Section 7: Algorithm approach to ACLS emergencies. *Circulation* 2000;102:136-165.

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NEPHROLOGY

ACID-BASE DISORDERS

Algorithmic Approach

- Draw serum chemistries and arterial blood gas (ABG) at the same time
- Check the serum pH
 - If $\text{pH} < 7.35 \rightarrow$ acidemia
 - If $\text{pH} > 7.45 \rightarrow$ alkalemia
- Does the direction of the Pco_2 explain the observed pH?
 - If yes $\rightarrow$ primary respiratory disorder
 - If no $\rightarrow$ primary metabolic disorder
 - Both may coexist

Respiratory Disorders

- Does the pH change 0.08 for every 10 mm Hg change in Pco_2 ?
 - If yes $\rightarrow$ primary acute respiratory disorder
 - If no $\rightarrow$ metabolic disturbance that is either compensatory or a second primary disorder
- Expected metabolic compensation for a respiratory acidosis¹
 - Acute: 1 mEq/L increase in HCO_3^- for every 10 mm Hg increase in Pco_2
 - Chronic: 4 mEq/L increase in HCO_3^- for every 10 mm Hg increase in Pco_2
 - HCO_3^- will rarely exceed 45 for pure compensatory purposes
- Expected metabolic compensation for a respiratory alkalosis¹

- Acute: 2 mEq/L decrease in HCO_3^- for every decrease of 10 mm Hg in Pco_2
- Chronic: 5 mEq/L decrease in HCO_3^- for every decrease of 10 mm Hg in Pco_2
- HCO_3^- will rarely fall below 12 for pure compensatory purposes
- If a primary respiratory disorder exists and the serum HCO_3^- does not fit between the acute/chronic expected values, then a second primary metabolic disturbance is present; if the serum HCO_3^- does fit within these values, then the metabolic component is compensatory

Metabolic Disorders

- Is there an anion gap (AG) present?
 - Its presence usually indicates a gap metabolic acidosis
 - However, the AG may also be increased by a loss of unmeasured cations, such as Ca^{2+} and Mg^{2+} , without implying the presence of an acidosis¹
 - The AG may be artificially decreased with the loss of unmeasured anion (e.g., hypoalbuminemia) or the gain of unmeasured cation (e.g., Li^{2+} , hypercalcemia, hypermagnesemia, increased globulin fraction)¹
- If an AG is present, calculate the delta gap (Δ gap = observed AG: 12)
 - Add Δ gap to observed serum HCO_3^-
 - If equal to normal serum $\text{HCO}_3^- \pm 2$, then no other metabolic disturbance is present
 - If less than normal serum $\text{HCO}_3^- \pm 2$, then a non-gap metabolic acidosis is present
 - If greater than normal serum $\text{HCO}_3^- \pm 2$, then a metabolic alkalosis is also present
- Expected respiratory compensation for metabolic acidosis¹
 - Winter's formula $\rightarrow ([1.5 \times \text{serum } [\text{HCO}_3^-]] + 8) \pm 2 = \text{expected } \text{Pco}_2$

- Values deviating from this level indicate the presence of a second primary respiratory disorder
- Generally, PCO_2 will not fall below 15 mm Hg for isolated compensation (i.e., levels below this imply a superimposed primary respiratory alkalosis)
- Expected respiratory compensation for a metabolic alkalosis¹
 - $\text{PCO}_2 = 15 + \text{HCO}_3^-$
 - Values deviating from this indicate an additional primary respiratory disorder
 - Isolated compensation rarely results in a $\text{PCO}_2 > 55$ mm Hg (i.e., levels above this imply a superimposed primary respiratory acidosis)

Metabolic Acidosis

Causes of AG Acidosis

- Methanol^{2,3}
 - Should suspect intoxication in presence of AG acidosis, nonspecific abdominal complaints, and blurred vision
 - Seizures, coma, renal failure, rhabdomyolysis, and pancreatitis may result
 - Toxicity is generally not manifested until 12-18 hours after ingestion
 - Laboratory studies: amylase, lipase, serum chemistries, creatine kinase, serum measured and osmolality calculated (osmolar gap), methanol and ethylene glycol levels, ABG
 - Often see elevated osmolar gap > 10
 - Treatment: see treatment specifics in Chapter 3
- Ethylene glycol^{2,3}
 - Should be suspected in the setting of an inebriated patient without the smell of alcohol and with a coexisting metabolic acidosis
 - Renal failure, adult respiratory distress syndrome, cardiovascular collapse, and rhabdomyolysis may result

- Laboratory studies: serum chemistries, osmolar gap, ABG, urinalysis, echocardiogram, and serum methanol and ethylene glycol levels
- Treatment: see treatment specifics in Chapter 3
- Alcoholic ketoacidosis²
 - Should be suspected in an alcoholic patient with abdominal pain, nausea, vomiting, and an anion gap acidosis
 - Classically occurs 1-3 days after an alcohol binge
 - Laboratory studies: serum chemistries, ABG, ethanol level, ethylene glycol and methanol levels, serum ketones, urinalysis
 - Treatment
 - Intravenous thiamine followed by volume resuscitation with dextrose additive
 - Careful electrolyte monitoring and repletion
- Diabetic ketoacidosis^{2,4,5}
 - Should be suspected in patient with blurred vision, polyuria, polydipsia, polyphagia, AG acidosis, ketonuria, and hyperglycemia
 - Look for any evidence of infection or myocardial ischemia as the exacerbating event
 - Laboratory studies: serum chemistries, complete blood count, urinalysis, chest x-ray, electrocardiogram (ECG)
 - Treatment:
 - Aggressive volume resuscitation
 - Intravenous insulin and glucose infusion
 - Electrolyte repletion
 - Sodium bicarbonate therapy generally not required with serum pH >7.15; evidence is controversial for bicarbonate therapy if pH is <7.15^{2,6}
- Lactic acidosis²
 - Should be suspected in the presence of hypoperfusion, liver failure, or internal organ ischemia
 - History and physical examination to identify possible etiology
 - Laboratory studies: serum chemistries, complete

blood count, coagulation studies, urinalysis, ABG, lactate level, chest x-ray, ECG

- Treatment:
 - Should be directed at underlying cause
 - Avoid sodium bicarbonate therapy unless pH <7.2
- Salicylate toxicity⁷
 - Suspect intoxication in patient with tinnitus, tachypnea, anion gap acidosis, and primary respiratory alkalosis
 - May see neurological depression, coma, liver or renal failure
 - Laboratory studies: serum chemistries, salicylate level, ABG
 - Treatment: see treatment specifics in Chapter 3
- Uremia
 - Should be suspected in patient with anasarca, abdominal discomfort, nausea, and loss of appetite
 - History may suggest renal failure
 - Laboratory studies: serum chemistries, ECG, chest x-ray
 - Treatment
 - Acutely control electrolyte imbalances
 - Sodium bicarbonate for pH <7.2
 - Hemodialysis

Non-AG Acidosis

- Rarely suspected on the basis of history and physical examination alone
- Presence of unexplained osteoporosis or nephrolithiasis (as seen in type I renal tubular acidosis [RTA]) may be clues to a chronic undiagnosed acidosis

Laboratory Studies

- Serum chemistries, ABG, urinalysis, urine electrolytes

- Urine AG (UAG) = $(U_{Na} + U_K) - U_{Cl}$
 - Negative UAG → loss of bicarbonate from either the stool or kidney (proximal type II RTA)
 - Positive UAG → defect in bicarbonate generation in the kidney

Causes of Non-Gap Acidosis⁸

- Type I (distal or classic) RTA
 - May see history of nephrolithiasis
 - Laboratory studies: non-gap acidosis, hypokalemia, positive UAG, urinary pH >5.5
 - Etiology:
 - Drugs and toxins: amphotericin B, toluene, trimethoprim, pentamidine
 - Genetic diseases: sickle cell disease, Wilson's disease, Ehlers-Danlos syndrome, hereditary ovalocytosis
 - Calcium disorders: Primary hyperparathyroidism, hypercalcemic hyperthyroidism, vitamin D intoxication, idiopathic hypercalciuria with nephrocalcinosis
 - Dysproteinemic states: nephrotic syndrome, cryoglobulinemia, amyloidosis
 - Autoimmune diseases: rheumatoid arthritis, Sjögren's syndrome, chronic active hepatitis, primary biliary cirrhosis, thyroiditis, fibrosing alveolitis
 - Renal diseases: renal transplant rejection, medullary sponge kidney, obstructive and reflex nephropathy
 - Treatment
 - Correction of acidosis with oral alkali therapy (i.e., citrate)
- Type II (proximal) RTA
 - Rarely suspected on the basis of history and physical examination alone
 - Laboratory studies: non-gap acidosis, negative UAG, hypokalemia common, variable urinary pH
 - May see evidence of other proximal tubular defects → Fanconi's syndrome (glycosuria, aminoaciduria, phosphaturia)

- Etiology
 - Fanconi's syndrome: multiple myeloma, light chain disease, Wilson's disease
 - Drugs and toxins: acetazolamide, outdated tetracyclines, aminoglycosides, valproate, ifosfamide, lead, mercury, 6-mercaptopurine
- Treatment
 - Discontinue any offending agents
 - Requires large amounts of alkali
 - Volume repletion, potassium repletion
 - May add thiazide diuretic to alter peritubular Starling's forces
- Type IV (hyperkalemic) RTA
 - Patients may present with manifestations of hyperkalemia
 - Most common causes include medication administration and advanced kidney disease
 - Laboratory studies: serum chemistries, urine electrolytes
 - Etiology includes anything that interferes with the production or action of the renin-angiotensin-aldosterone axis:
 - Medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, pentamidine, triamterene, trimethoprim, amiloride, spironolactone, heparin, azole antifungals, cyclosporine A
 - Renal diseases: tubular interstitial disease, diabetic nephropathy, systemic lupus erythematosus, HIV nephropathy, obstructive uropathy, medullary cystic disease, renal transplant rejection, chronic kidney disease
 - Adrenal insufficiency
 - Treatment
 - Discontinue offending medication
 - Control hyperkalemia
 - Oral alkali therapy if acidosis persists in setting of chronic kidney disease
- Acidosis of chronic kidney disease

- Presents as non-gap acidosis in presence of chronic renal failure
- Potassium is normal in contrast to type IV RTA
- Treatment:
 - Alkali therapy to keep serum HCO_3^- between 22 and 26

Metabolic Alkalosis^{9,10}

Saline Responsive

- Metabolic alkalosis in the presence of low effective arterial blood volume
- History should focus on symptoms of volume loss or gain
- Physical examination should focus on evaluation of volume status
- Laboratory studies: serum chemistries, ABG, low urinary chloride (unless patient taking diuretic)
- Etiology
 - Loop or thiazide diuretics
 - Vomiting, nasogastric suctioning
 - Nonreabsorbable anions such as penicillin or carbenicillin in setting of volume depletion
 - Posthypercapnia
 - Liddle's syndrome: suspect in a hypertensive patient with low serum potassium
- Treatment
 - Discontinuation of offending agent
 - Control vomiting
 - Volume repletion, electrolyte repletion
 - Acetazolamide for posthypercapnic metabolic alkalosis

Saline Unresponsive

- Metabolic alkalosis in the presence of a normal-to-increased effective arterial blood volume
- Generally seen in the presence of true or apparent mineralocorticoid excess

- Physical examination often reveals a blood pressure that is high or high-normal; patient will be euvolemic
- Laboratory studies: serum chemistries, ABG, urinary chloride will be elevated; check spot serum aldosterone and renin levels with patient supine for 30 minutes
 - High renin, high aldosterone
 - Renovascular hypertension: treat with potassium-sparing diuretic, K^+ repletion
 - Renin-secreting tumor: treat with K^+ repletion, potassium-sparing diuretic, surgical excision
 - Low renin, high aldosterone
 - Hyperaldosteronism (Conn's syndrome): treat with spironolactone, K^+ repletion, adrenalectomy if refractory or malignant



Patient Care Warnings

- To correct AG for hypoalbuminemia, add 2.5 for every decrease of 1 g/dL in serum albumin
- In the late stages of methanol poisoning, the osmolar gap may not be elevated: therefore, an absence of an elevated osmolar gap does not rule out methanol intoxication
- Continue to monitor electrolytes after dialysis in methanol intoxication: rebound can occur frequently
- The presence of calcium oxalate stones in urinalysis may suggest ethylene glycol intoxication
- In general, alkalemia ($pH > 7.6$) is life-threatening and far more dangerous than an acidosis: this should be treated with permissive hypercapnia (if on mechanical ventilation) and HCl administration if necessary⁸

- Low renin, low aldosterone
 - Liddle's syndrome
 - Licorice
- Other causes: magnesium deficiency, potassium deficiency, milk-alkali syndrome

References

- ① 1. DuBose TD. Acid-base disorders. In Levine, SA, ed. *Brenner & Rector's The Kidney*. 7th ed. Philadelphia, WB Saunders, 2004:930.
- ① 2. White SR, Rosnik T. Toxic alcohols. In Marx JA, ed. *Rosen's Emergency Medicine*. 5th ed. St. Louis, Mosby, 2002:2127-29.
- ① 3. DuBose TD. Acid-base disorders. In Levine, SA, ed. *Brenner & Rector's The Kidney*. 7th ed. Philadelphia, WB Saunders, 2004:961-69.
- ② 4. Androgué HJ, Wilson H, Boyd AE, et al. Plasma acid-base patterns in diabetic ketoacidosis. *N Engl J Med* 1982;307:1603-10.
- ② 5. Okuda Y, Androgué HJ, Field JB, et al. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. *J Clin Endocrin Metab* 1996;81:314-20.
- ① 6. Hood VL, Tannen RL. Protection of acid-base balance by pH regulation of acid production. *N Engl J Med* 1998;339:819-26.
- ① 7. Androgué HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998;338:26-33.
- ① 8. Soriano JR. Renal tubular acidosis: The clinical entity. *J Am Soc Nephrol* 2002;13:2160-70.
- ① 9. Androgué HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998;338:107-11.
- ① 10. DuBose TD. Acid-base disorders. In Levine, SA, ed. *Brenner & Rector's The Kidney*. 7th ed. Philadelphia, WB Saunders, 2004:969-76.

HYPERNATREMIA

Definition, Etiology, and Epidemiology

- Generally defined as a serum sodium (Na^+) greater than 145 mmol/L (definition varies with laboratory)
- Represents excessive loss of water in relation to body sodium stores¹
- Commonly observed in patients whose access to free water is impaired (e.g., the elderly, very young, and nursing home residents)

- Less often, results from administration of hypertonic solutions

ETIOLOGIES		
Pure Water Loss	Hypotonic Fluid Loss	Hypertonic Sodium Gain
Insensible losses (fever) Hypodipsia Central diabetes insipidus Tumor Trauma Histiocytosis Tuberculosis Sarcoidosis Aneurysms Meningitis Encephalitis Guillain-Barré syndrome Nephrogenic Diabetes Insipidus Hypercalcemia Hypokalemia Lithium Demeclocycline Amphotericin B	Loop diuretics Osmotic diuresis (mannitol, urea, glucose) Postobstructive diuresis Polyuric phase of acute tubular necrosis Vomiting/nasogastric drainage Enterocutaneous fistula Diarrhea Burns Excessive sweating	Hypertonic feeding preparation Hypertonic bicarbonate infusion Hypertonic saline infusion Ingestion of sea water Hypertonic saline enemas Cushing's syndrome Primary aldosteronism

Pearls of the History and Physical Examination

- Symptoms include impaired consciousness, weakness, and confusion, all of which are correlated with the severity of disease; thirst is usually present and profound but may be absent in the elderly¹
- Physical examination is generally used to look for signs of volume depletion such as dry mucous

membranes, flat neck veins, and increased skin turgor

Diagnostic Studies and Laboratory Values

- Serum chemistries, serum osmolality, and urine osmolality
- Urine osmolality should be elevated in hypernatremia; if the urine osmolality is <150 mOsm/kg, suspect a deficit in antidiuretic hormone (i.e., diabetes insipidus)

Guide to Acute Management¹

- Discontinue any aggravating factors.
- Calculate the expected fall in serum Na^+ in response to 1 L of a given infusate (see next section for formula); consider ongoing fluid losses
- Rate of infusion is dictated by the speed of recovery desired; if the hypernatremia has developed over hours (hypertonic infusate), then a correction of 1 mmol/L in the serum Na^+ is acceptable with no daily maximum; if the duration is unknown or the condition is chronic, reduction should be at a rate of 0.5 mmol/L/hr, with a maximum of 10 mmol/L/d
- The infusate chosen depends on the clinical setting; if pure water loss is present, then a D_5W infusion is appropriate; if volume depletion is suspected, then 0.45% or 0.2% saline should be used; in the setting of hypertonic sodium gain, loop diuretics should be administered along with D_5W
- In general, the use of 0.9% saline (normal saline) or lactated Ringer's solution should be avoided unless there is evidence of circulatory compromise; even in this instance, 0.9% saline should be administered only until hemodynamic stability is achieved, followed by the infusion of 0.45% saline
- Once corrected, continuous administration of free water either by IV or oral route is continued to maintain serum sodium



Patient Care Warnings

- Overly rapid correction of hypernatremia can be just as problematic as for hyponatremia; monitor laboratory results frequently during correction to avoid cerebral edema²

References

- ③ 1. Adrogué HJ, Madias NE. Hyponatremia. *New Engl J Med* 2000;342:1493-99.
- ② 2. Lien YH, Shapiro JI, Chan L. Effects of hypernatremia on organic brain osmoles. *J Clin Invest* 1990;85:1427-35.

HYPONATREMIA

Definition, Etiology, and Epidemiology

- Generally defined as serum sodium (Na^+) less than 130 mmol/L (definition varies with laboratory)
- Common electrolyte disorder with a prevalence of 2.5% in hospitalized patients¹
- Represents an excess of free water in relation to body stores; may occur in any volume state

ETIOLOGY		
Hypovolemia	Euvolemia	Hypervolemia
Renal sodium losses Diuretics Osmotic diuresis (urea, mannitol, glucose)	Central nervous system Trauma Hemorrhage Mass lesion Stroke	Congestive heart failure (either severe or during aggressive diuresis) Cirrhosis Nephrotic syndrome

(Continued on following page)

ETIOLOGY (Continued)

Hypovolemia	Euvolemia	Hypervolemia
Adrenal insufficiency	Inflammatory and demyelinating diseases	Renal failure
Bicarbonaturia (either type II RTA or vomiting)	Drugs	Pregnancy
Ketonuria	Thiazide diuretics*	
Nonrenal sodium losses	Desmopressin	
Diarrhea	Oxytocin	
Vomiting	Nicotine	
Blood loss (severe)	Phenothiazines	
Fluid sequestration	Selective serotonin reuptake inhibitor antidepressants	
Peritonitis	Tricyclic antidepressants	
Bowel obstruction	Opiate derivatives	
Pancreatitis	Vincristine	
Burns	Carbamazepine	
	Cyclophosphamide	
	Pulmonary	
	Respiratory failure	
	Positive pressure ventilation	
	Decreased solute intake	
	Beer potomania	
	Tea and toast diet	
	Other	
	Hypothyroidism	
	Adrenal insufficiency	
	Syndrome of inappropriate antidiuretic hormone secretion†	
	Postoperative state	
	HIV infection	
	Excessive water intake‡	

*Thiazide diuretics can cause hypovolemic or euvolemic hyponatremia

†SIADH is a diagnosis of exclusion and can be made only in the setting of euvolemia

‡In the normal kidney, a minimum of 15-20 L of free water a day is required to cause hyponatremia; this threshold, however, is reduced if renal failure is present or if solute intake is low

Pearls of the History and Physical Examination

- Symptoms include headache, nausea, vomiting, cramps, lethargy, disorientation, seizures, coma, and brainstem herniation²; most hyponatremia, however, is mild and asymptomatic
- Thoroughly review recent events (e.g., surgery), volume assessment, and medications
- On physical examination, determination of volume status and neurological assessment should be performed in order to determine cause and assess severity

Diagnostic Studies and Laboratory Values

- Serum chemistries, serum osmolality, urine electrolytes, and urine osmolality
- If serum osmolality is normal in the setting of hyponatremia, this implies three possibilities:
 - Administration of an iso-osmotic solution that does not contain NaCl (e.g., glycine irrigation during transurethral resection of the prostate)
 - High serum glucose or high mannitol
 - Pseudohyponatremia as a result of elevated triglycerides or total protein³
- A low serum osmolality, in the setting of a low serum Na^+ , indicates true hyponatremia
- Urine osmolality $>150\text{--}200$ mOsm/kg, in the setting of hyponatremia, implies an excess of antidiuretic hormone (may be appropriate) and inappropriate urinary concentration
- Urine osmolality <100 mOsm/kg implies excessive water intake or low solute intake

Guide to Acute Management¹

- No matter what the initial serum Na^+ level is, urgent treatment is not indicated unless severe neurological symptoms such as seizure or coma are present; this would be very rare for any $\text{Na}^+ >125$ mmol/L

- Treatment is limited to that of the underlying disorder; water restriction in the euvolemic and hypervolemic patient is undertaken, whereas volume repletion is the goal for the hypovolemic patient
- In the presence of seizures or coma, hypertonic (3%) saline should be administered; loop diuretics should also be considered if the patient is euvolemic or hypervolemic, in order to prevent volume overload
- To correct hyponatremia, the amount of saline to be infused is calculated according to the following formula:

$$(\text{Infusate Na}^+ - \text{Serum Na}) / (\text{Total Body Water} + 1)$$

- The total body water is $0.6 \times \text{weight (kg)}$ for nonelderly men, $0.5 \times \text{weight (kg)}$ for nonelderly women, $0.5 \times \text{weight (kg)}$ for elderly men, and $0.45 \times \text{weight (kg)}$ for elderly women
- Infusate Na is determined depending on the fluid utilized, as follow:
 - 5% saline = 855
 - 3% saline = 513
 - 0.9% saline (normal saline) = 154
 - Lactated Ringer's = 130
 - 0.45% saline (1/2 normal saline) = 77
 - 0.2% saline = 34
 - D₅W = 0
- The formula determines how much 1 L of any given saline infusate will increase the serum sodium concentration; the rate of the infusion is then calculated from the rate of correction desired
- Initial goal of correction in a patient with neurological signs/symptoms should be 1-2 mmol/L/hr, with frequent laboratory checks and infusion rate adjustment as necessary; once the patient is no longer showing severe signs/symptoms of hyponatremia, any hypertonic infusion should be discontinued
- In the absence of neurological signs/symptoms, treatment is fluid restriction (for euvolemia), volume

administration (for hypovolemia), or diuresis (for volume overload)



Patient Care Warnings

- Correction of hyponatremia should not exceed 8-10 mmol/L/d; overly aggressive correction could result in central pontine myelinolysis

References

- ③ 1. Adroque HJ, Madias NE. Hyponatremia. *New Engl J Med* 2000;342:1581-89.
- ③ 2. Strange K. Regulation of solute and water balance and cell volume in the central nervous system. *J Am Soc Nephrol* 1992;3:12.
- ③ 3. Weisberg LS. Pseudohyponatremia: A reappraisal. *Am J Med* 1989;86:315-18.

HYPERKALEMIA

Definition, Etiology, and Epidemiology

- Generally defined as potassium (K^+) greater than 5.5 mmol/L (definition varies with laboratory)
- Occurs in 1%-10% of all patients, resulting in a mortality rate of 14%-40%¹
- Most commonly caused by medications and renal failure, often together
- Etiology includes:
 - Pseudohyperkalemia: fist clenching, severe thrombocytosis ($>1,000,000$) or leukocytosis, in vitro hemolysis²
 - Metabolic acidosis
 - Diabetes (low renin state)
 - Lack of insulin and increased tonicity

- Overly aggressive K^+ supplementation
- Muscle necrosis, lactic acidosis (cell death with K^+ leakage)
- Massive red blood cell transfusion
- Tumor lysis syndrome
- Medications: succinylcholine, mannitol, alpha agonists, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, digoxin toxicity (poisons Na-K ATPase), heparin (interferes with aldosterone biosynthesis in IV or SQ forms), ketaconazole, potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs, cyclosporine and tacrolimus (block aldosterone action by tubulointerstitial fibrosis, may induce hyporeninemic hypoaldosterone state), pentamidine, trimethoprim
- Adrenal insufficiency
- Systemic lupus erythematosus
- Amyloidosis
- Sickle cell anemia, hemolytic anemia
- Renal failure

Pearls of the History and Physical Examination

- Rarely suspected on the basis of history and physical examination; first manifestation of hyperkalemia may often be cardiac arrest
- Signs and symptoms may develop at relatively low levels if serum ionized calcium is low
- If hyperkalemia develops acutely or in the hospital, medication administration or acute renal failure is almost always the cause

Diagnostic Studies and Laboratory Values

- Chemistries with albumin and/or ionized calcium, complete blood count (hemolysis), urine electrolytes (transtubular potassium gradient [TTKG]; see the next section on hypokalemia), and electrocardiogram (ECG)

- TTKG >8 in the setting of hyperkalemia implies normal tubular function and increased release of K^+ (rhabdomyolysis, hemolysis, or tumor lysis)³
- TTKG <8 in the setting of hyperkalemia implies decreased tubular excretion of K^+ , most commonly related to medications or renal failure; if no obvious cause, consider adrenal insufficiency³
- Classic ECG progression¹:
 - K^+ 5.5-6.5: peaked T waves
 - K^+ 6.5-8.0: prolonged PR interval, widened QRS complex, decreased P waves
 - K^+ >8.0 : loss of P waves, bundle branch block, sinusoidal pattern, cardiac arrest
- If serum ionized calcium is low, then the ECG changes may occur at K^+ levels lower than indicated above

Guide to Acute Management^{1,4}

- If ECG changes are present, 1 amp of calcium chloride or gluconate should be given; repeat if ECG changes persist or recur; onset of action is 2-3 minutes and lasts 30-60 minutes
- If K^+ >6.5 without ECG changes, give (1) 10 units IV insulin, followed by 1 amp. of D_{50} solution: onset in 10-20 minutes, peak at 30-60 minutes; lasts 4-6 hours, (2) 10-20 mg nebulized albuterol given over 10 minutes: effect starts in 30 minutes, peaks at 90 minutes, lasts 4-6 hours; monitor blood glucose levels frequently to avoid significant hypoglycemia
- Bicarbonate has little role unless the pH is <7.2 and should be discontinued as treatment once this level is reached
- Should also give therapy to decrease total body K^+ stores:
 - Loop diuretics, provided volume status is appropriate
 - Kayexalate 15-30 g po or pr

- Consider hemodialysis if K^+ remains elevated or patient unstable
- Consider the cause of hyperkalemia once the patient is stabilized; remove offending medications, give glucocorticoids + fludrocortisone for adrenal insufficiency, etc.



Patient Care Warnings

- ECG changes are not sensitive for cardiac toxicity and can progress rapidly when present; even moderately elevated K^+ levels should be treated aggressively
- ECG changes should be suspected at lower K^+ levels if the serum ionized calcium is low
- Calcium chloride should always be given through a central line
- Avoid calcium use in patients with hyperkalemia in the setting of digoxin toxicity as this may exacerbate cardiac arrhythmias
- Take care when administering Kayexalate in the immediate postoperative phase and to patients with ileus/obstruction: this can result in intestinal necrosis

References

- ③ 1. DuBose TD. Acid-base disorders. In Levine SA, ed. Brenner & Rector's The Kidney, 7th ed. Philadelphia, WB Saunders, 2004: 1005-25.
- ③ 2. Wiederkehr MR, Moe OW. Factitious hyperkalemia. *Am J Kidney Dis* 2000;36:1049-53.
- ③ 3. Ethier JH, Kamel KS, Magner PO, et al. The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. *Am J Kidney Dis* 1990;15:309-15.
- ③ 4. Gennari FJ. Disorders of potassium homeostasis: Hypokalemia and hyperkalemia. *Crit Care Med* 2002;18:1-15.

HYPOKALEMIA

Definition, Etiology, and Epidemiology

- Generally defined as potassium (K^+) less than 3.6 mmol/L (definition varies with laboratory)
- Found in as many as 20% of hospitalized patients¹
- Most common causes are medication administration and gastrointestinal (GI) losses
- Etiology can be divided into cellular shifts, renal losses, and GI losses^{1,2}

ETIOLOGY		
Renal Losses	Cellular Shifts	Stool Losses
Drugs Acetazolamide* Loop diuretics Thiazide diuretics Fludrocortisone Aminoglycosides† Cisplatin Foscarnet Amphotericin B† Penicillin and its derivatives	Beta agonists Epinephrine Decongestants (in overdose) Bronchodilators Tocolytics Theophylline Caffeine Verapamil intoxication (no effect at therapeutic doses) Insulin overdose Chloroquine overdose	Diarrhea from any cause*
Endocrine Saline-unresponsive metabolic alkalosis (see the first section on Acid-Base Disorders in this chapter) Diabetic ketoacidosis		

(Continued on following page)

ETIOLOGY (Continued)**Renal Losses****Cellular Shifts****Stool Losses****Metabolic**

Magnesium
deficiency

Types I and II renal
tubular acidosis (RTA)

Vomiting/nasogastric
suction

Other:

Accelerated, malignant
hypertension

*Unlike the other diuretics listed, acetazolamide will cause RTA, not alkalosis

†Classically associated with a type I RTA but also causes proximal tubular damage and thus may cause a type II RTA as well

Pearls of the History and Physical Examination

- Most patients will present at $K^+ > 3.0$ mmol/L, a level at which signs and symptoms are rarely present
- Between 3.0 and 2.5 mmol/L, generally nonspecific signs and symptoms related to muscle weakness may be present
- Below 2.5 mmol/L, profound weakness, paralysis, and muscle necrosis may occur: these are neither specific nor sensitive findings
- Ventricular arrhythmias can develop at any level of hypokalemia when associated with a myocardial infarction, in a patient with previously damaged heart, or with concomitant digoxin intoxication: cardiac manifestations are, however, very rare in patients without structural heart disease

Diagnostic Studies and Laboratory Values

- Urine and serum electrolytes: transtubular potassium gradient (TTKG) may be calculated³

- $\text{TTKG} = [\text{urine potassium } (U_k)/\text{plasma potassium } (P_k)] \times [\text{plasma osmolality } (P_{\text{osm}})/\text{urine osmolality } (U_{\text{osm}})]$
- $U_k > 20$ or $\text{TTKG} > 2$ in the setting of hypokalemia implies inappropriately high renal losses; otherwise, cellular shifts or correction of renal losses are implied
- 12-lead electrocardiogram is generally not needed unless cardiac manifestations are suspected
- Renin and aldosterone levels should be determined if saline-unresponsive metabolic alkalosis is present

Guide to Acute Management^{2,4}

- As a rule, every 0.3 mmol/L decrease in serum potassium represents a loss of 100 mEq of body stores (assuming cellular shifts are not contributing)
- Management begins with removing any offending medication
- Volume should be adequately repleted if clinically indicated; should consider the addition of K^+ to the replacement fluids to avoid further hypokalemia



Patient Care Warnings

- Hyperkalemia is usually more life-threatening than hypokalemia
- As treatment of hypokalemia is rarely emergent, intravenous potassium repletion should be limited use in truly urgent situations
- Intravenous potassium should be administered at a rate not to exceed 20 mEq/hr with cardiac monitoring; >60 mEq should not be given without rechecking serum K^+ levels

- Intravenous K^+ is used only if the serum K^+ is <2.5 mmol/L, if there is evidence of muscle necrosis, and in the presence of a digoxin-toxic rhythm or ventricular arrhythmia; the goal should be to raise the serum K^+ level to 4.0 mmol/L in these cases
- In all other situations, K^+ repletion is best done orally with high-potassium foods or oral supplements.

References

1. Gennari FJ. Hypokalemia. *New Engl J Med* 1998;339:451-58.
2. Gennari FJ. Disorders of potassium homeostasis: Hypokalemia and hyperkalemia. *Crit Care Med* 2002;18:1-15.
3. Ethier JH, Kamel KS, Magner PO, et al. The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. *Am J Kidney Dis* 1990;15:309-15.
4. DuBose TD. Acid-base disorders. In Levine SA, ed. *Brenner & Rector's The Kidney*, 7th ed. Philadelphia, WB Saunders, 2004: 1005-06.

HYPERMAGNESEMIA

Definition, Etiology, and Epidemiology¹

- Generally defined as an elevation of the serum magnesium above 1.8 mEq/L
- Renal failure is a common cause of hypermagnesemia, especially when intake is even mildly increased
- Etiologies
 - Renal failure with glomerular filtration rate (GFR) <20 mL/min in the setting of significantly increased intake with oral antacids and cathartics¹
 - Intravenous (IV) repletion of hypomagnesemia
 - IV therapy for preeclampsia
 - Toxicity from oral magnesium salts is enhanced

by bowel obstruction, inflammatory bowel disease, and bowel perforation

Pearls of the History and Physical Examination

- Symptoms are rare at serum levels <4 mEq/L.
- Hypotension, nausea, vomiting, and ileus are usually the first manifestations; these are often followed by flaccid muscular paralysis, bradyarrhythmias (sinus, junctional, or high-grade atrioventricular block), respiratory depression, coma, and cardiac arrest

Diagnostic Studies and Laboratory Values

- Serum chemistries

Guide to Acute Management²

- In the setting of mild hypermagnesemia (i.e., <4 mEq/L) or absence of symptoms, treatment is aimed at discontinuation of supplements
- In the presence of symptoms or electrocardiogram changes, magnesium antagonism should be induced with 1 g IV calcium chloride or gluconate over 2-5 minutes
- If renal function is adequate, magnesium stores can be decreased with the use of loop diuretics; assure adequate volume status, and continue to monitor
- If renal function is significantly impaired (GFR <30 mL/min) or if diuresis is not adequate with conventional doses, then dialysis may be required to remove magnesium

References

- ② 1. Randall RE, Cohen MD, Spray CC. Hypermagnesemia in renal failure: Etiology and toxic manifestations. *Ann Intern Med* 1964;61:73-88.
- ③ 2. DuBose TD. Acid-base disorders. In Levine SA, ed. *Brenner & Rector's The Kidney*, 7th ed. Philadelphia, WB Saunders, 2004: 1057-58.

HYPOMAGNESEMIA

Definition, Etiology, and Epidemiology

- Generally defined as a serum magnesium <1.4 mEq/L; however, correlation between total body stores and serum levels is very poor
- Hypomagnesemia is present in 10%-50% of hospitalized patients depending on the series and severity of illness and comorbidities¹

ETIOLOGIES

Nonrenal Wasting	Renal Wasting
Nutritional deficiency*	Postacute tubular necrosis diuresis
Chronic alcohol use†	Postobstructive diuresis
Refeeding syndrome	Osmotic diuresis
Whipple's disease	Chronic volume expansion
Inflammatory bowel disease	Hyperaldosteronism
Fat malabsorption	Loop diuretics
Chronic diarrhea even without malabsorption	Thiazide diuretics
	Hypercalcemia
	Cyclosporine
	Tacrolimus
	IV pentamidine
	Carboplatinum
	Amphotericin B
	Aminoglycosides
	Bartter's syndrome (defect in paracellular protein)
	Gitelman's syndrome

*Rare in the United States when enteral feedings are tolerated for a significant period

†Although alcoholics have poor nutritional intake, alcohol also induces renal wasting

Pearls of the History and Physical Examination

- When severe, hypomagnesemia may result in neuromuscular manifestations such as weakness, tetany,

seizures, paresthesias, vertical and horizontal nystagmus, and Trousseau's and Chvostek's signs.

- Like other electrolyte abnormalities, it is not common for diagnosis to be suspected from the history and physical examination

Diagnostic Studies and Laboratory Values

- Serum chemistries; electrocardiogram to assess for QT prolongation
- Hypokalemia can occur in the setting of hypomagnesemia due to impaired energetics of the thick ascending limb (as if the patient is taking lasix)
- Hypocalcemia may develop due to decreased parathyroid hormone (PTH) production and peripheral insensitivity to PTH²
- If the diagnosis is unclear, check 24-hour urine for magnesium; in the setting of hypomagnesemia, a level of >24 mg/24 hr implies renal magnesium wasting
- If a 24-hour urine cannot be obtained, the fractional excretion of magnesium ($U_{Mg}/P_{Mg} \times P_{Creat}/U_{Creat}$) indicates magnesium wasting if >1%

Guide to Acute Management³

- Treatment is generally not necessary unless symptoms, significant seizure disorder, active cardiac disease, severe hypocalcemia and hypokalemia, or severe hypomagnesemia <1.4 mg/dL are present
- In an emergent situation, 2 g of magnesium sulfate can be administered intravenously over 2-4 minutes
- In a less urgent situation, a slower rate is safer and more efficient; 8 g may be administered over 24 hours, followed by 4 g over 2-4 days
- Alternatively, once serum magnesium is normalized and symptoms resolve, oral magnesium can be instituted

- If losses are ongoing once magnesium has been repleted, oral supplements should be used



Patient Care Warnings

- Unless magnesium repletion urgently needed, always attempt to treat hypomagnesemia via oral supplementation: this is more favorably reabsorbed by the kidney
- Attempt to keep magnesium levels ≥ 2.0 mg/dL in the patient with active cardiac disease

References

- ② 1. Wong ET, Rude RK, Singer FR, et al. A high prevalence of hypomagnesemia and hypermagnesemia in hospitalized patients. *Am J Clin Pathol* 1983;79:349-52.
- ② 2. Freitag JJ, Martin KJ, Conrades MB, et al. Skeletal resistance to parathyroid hormone in magnesium deficiency: Studies in isolated perfused bone. *J Clin Invest* 1979;64:1238-44.
- ③ 3. DuBose TD. Acid-base disorders. In Levine SA, ed. *Brenner & Rector's The Kidney*, 7th ed. Philadelphia, WB Saunders, 2004: 1051-57.

HYPERPHOSPHATEMIA

Definition, Etiology, and Epidemiology

- Generally defined as a serum phosphate >5.0 mg/dL
- Most common cause is chronic renal failure
- Etiologies include renal insufficiency, tumor lysis syndrome, hypoparathyroidism, acromegaly, respiratory acidosis, phosphate enemas, and intravenous phosphate (the last two are rare causes when the glomerular filtration rate is >25 mL/min)

Pearls of the History and Physical Examination

- Most common findings, if any, are signs and symptoms of hyperphosphatemia-induced hypocalcemia
- In addition, necrotic and painful ulcers (calciophylaxis) may result if the calcium phosphate product is >70
- Hyperphosphatemia is rarely suspected on the basis of history and physical examination

Diagnostic Studies and Laboratory Values

- Serum chemistries
- Lactate dehydrogenase, complete blood count if tumor lysis is suspected
- Parathyroid hormone level if parathyroid disorder suspected

Guide to Acute Management¹

- Unless associated with tumor lysis syndrome, rarely is treatment an urgent undertaking



Patient Care Warnings

- Bicarbonate should be used with caution in tumor lysis syndrome: this can result in precipitation if the calcium phosphate product is >70 ; if acidosis is a continuing problem in this setting, then dialysis needs to be considered
- Avoid phosphate enemas in end-stage renal disease patients: this can result in calciophylaxis or seizures resulting from acute hypocalcemia

- Management is generally with dietary restriction and, if persistent, with the use of phosphate binders
- If the calcium phosphate product is >70 , then either aluminum hydroxide or Renajel should be used; if under this threshold, then calcium acetate can be used
- In the absence of renal failure, intravenous fluids and acetazolamide may help to increase excretion
- In case of tumor lysis, treatment starts with fluids and control of electrolytes
- If renal failure is a significant feature, hemodialysis should be considered

Reference

- ③ 1. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2001;39:S1.

HYPOPHOSPHATEMIA

Definition, Etiology, and Epidemiology

- Generally defined as a serum phosphate <2.5 mg/dL, with severe hypophosphatemia defined as a level <1.0 mg/dL¹
- Common problem in hospitalized patients¹
- Etiologies include hyperparathyroidism, volume expansion, vitamin D deficiency, hypomagnesemia, Fanconi's syndrome, postrenal transplant, acetazolamide use, diabetic ketoacidosis (insulin) treatment, inadequate dietary intake, chronic diarrhea, phosphate-binding antacids, chronic alcoholism, respiratory alkalosis, postparathyroidectomy (hungry bone syndrome)

Pearls of the History and Physical Examination

- Generally, patients with phosphate levels >1.0 mg/dL are asymptomatic

- Below 1.0 mg/dL, there is a predisposition to hemolytic anemia as well as decreased efficiency of red blood cell oxygen-carrying capacity²; muscle weakness, including failure of the respiratory and cardiac muscles, may occur
- Rhabdomyolysis can occur with very low levels of serum phosphate³
- Lactic acidosis can result with severe hypophosphatemia (results in decreased 2,3-DPG, which shifts the hemoglobin-oxygen dissociation curve to the left)⁴
- Can observe diminished phagocytosis by polymorphonuclear cells, diminished platelet function, and diminished central nervous system function as a result of decreased cellular adenosine triphosphate production
- Most patients are asymptomatic

Diagnostic Studies and Laboratory Values

- Serum chemistries: low calcium, magnesium, potassium, and phosphate suggest poor intake and/or alcoholism
- If diagnosis is not clear, a parathyroid hormone level should be drawn
- Urinalysis to assess for glycosuria $\pm$ 24-hour urine for aminoaciduria and phosphate excretion if Fanconi's syndrome (type II renal tubular acidosis) is suspected

Guide to Acute Management

- If phosphate is >1.0 mg/dL without symptoms, then repletion can be achieved orally with low-fat milk; if this cannot be tolerated or if more supplementation is needed, then Neutraphos or K-Phos can be used with meals⁵
- If phosphate is <1.0 mg/dL without symptoms, then intravenous repletion is indicated at 2.5 mg/kg over 6 hours⁵

- If symptoms are present, then 5 mg/kg over 6 hours should be used

References

- ② 1. Halevy J, Bulvick S. Severe hypophosphatemia in hospitalized patients. *Arch Intern Med* 1985;148:153-55.
- ② 2. Klock JC, Williams HE, Mentzer WC. Hemolytic anemia and somatic cell dysfunction in severe hypophosphatemia. *Arch Intern Med* 1974;134:360-64.
- ② 3. Knochel JP. Hypophosphatemia and rhabdomyolysis. *Am J Med* 1992;92:455-57.
- ② 4. Travis SF, Sugerman HJ, Ruberg RL, et al. Alterations of red-cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation. *N Engl J Med* 1971;285:763-68.
- ③ 5. DuBose TD. Acid-base disorders. In Levine SA, ed. *Brenner & Rector's The Kidney*, 7th ed. Philadelphia, WB Saunders, 2004: 1060-64.

ACUTE RENAL FAILURE

General Overview

Definition, Etiology, and Epidemiology¹⁻⁵

- Acute renal failure (ARF) generally defined as a rise in serum creatinine of 0.5 mg/dL above baseline or a decline in glomerular filtration rate (GFR) of 50% over hours to weeks; there is no formally accepted definition
- Divided into:
 - Prerenal azotemia: 50%-60%
 - Intrinsic renal disease: 35%-40%
 - Postrenal obstruction: <5%
- ARF complicates about 5% of all admissions to the hospital and 30% of intensive care unit (ICU) admissions; it is an independent negative prognostic factor for mortality
- Consequences of renal failure include volume over-

load, solute excess (e.g., hyperkalemia, acidosis, hyperphosphatemia, uremia), sepsis, bleeding, and respiratory failure

Pearls of the History and Physical Examination¹⁻⁵

- History should focus on:
 - Hemodynamic insults (hypotension or volume overload) and exposure to nephrotoxins
 - Signs or symptoms of infection, third spacing, congestive heart failure (CHF), or myocardial ischemia
 - Acute anuria, which may suggest urinary obstruction
- Physical examination should include orthostatic vital signs, skin turgor, presence or absence of elevated jugular venous pressure, S₃ gallop, pulmonary rales, ascites, and edema
- Obtain a postvoid residual (PVR), especially in older men due to risk of benign prostatic hypertrophy (BPH)

Diagnostic Studies and Laboratory Values¹⁻⁵

- Serum chemistries, complete blood count, urinalysis with microscopy, urine sodium, urine creatinine
- Radiological examination should include renal ultrasound to rule out obstruction, $\pm$ chest x-ray to evaluate for pulmonary edema

Guide to Acute Management¹⁻⁶

- Initial management should include reversing cardiovascular insults and electrolyte abnormalities
- Ensure adequate oxygenation with supplemental oxygen, diuretics, and invasive or noninvasive mechanical ventilation if indicated
- Intravenous (IV) fluid challenge for volume depletion with normal saline
- Evaluate for the presence of an indication for

emergent hemodialysis (see the section, Overview and Indications for Renal Replacement Therapy)

- Discontinue all potential nephrotoxins, and adjust dosage of other medications based on GFR
- Transfuse packed red blood cells (RBCs) as needed for symptomatic anemia or cardiovascular instability
- Gastrointestinal (GI) prophylaxis with H₂ blockers or proton pump inhibitors due to increased risk of bleeding from dysfunctional platelets that occur with uremia
- Consider desmopression (ddAVP) for uncontrolled bleeding secondary to dysfunctional platelets

Prerenal Azotemia^{7,8}

- Most frequent cause of ARF
- Due to a decrease in glomerular perfusion, usually from decreased effective arterial blood volume

Etiology

- Hypovolemia: blood loss; volume loss from GI tract, kidneys, respiratory tract, skin
- Cardiac failure: myocardial or valvular dysfunction, cardiac tamponade
- Systemic vasodilation: cirrhosis, sepsis, medications, anesthesia, anaphylaxis
- Impaired renal autoregulation of blood flow
 - Afferent arteriolar vasoconstriction from non-steroidal anti-inflammatory drugs (NSAIDs), cyclosporine, amphotericin, radiocontrast dye, hypercalcemia, sepsis
 - Efferent arteriolar vasodilation from angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs)

History and Physical Examination Findings

- Assess for signs of volume loss, infection, orthostasis, cardiac failure, or recent insults (medication changes, pancreatitis, surgery) by history
- Physical examination should focus on assessment of volume status, i.e., orthostatic vital signs

Laboratory Findings

- Usually see elevated serum blood urea nitrogen (BUN) to creatinine ratio ($>20:1$)
- Bland urinary sediment: may see some hyaline casts
- $\text{FeNa} < 1\%$

Management

- Reversal of hemodynamic insult
- Volume depletion/third spacing: isotonic saline is equal to or higher than colloid in critically ill patients with prerenal insufficiency
- Volume overload [increased extracellular fluid (ECF) but with decreased effective arterial blood volume] - sodium restriction
- Diuretics: if used, goal net diuresis of 1 L/d to avoid hemodynamic compromise (escalating therapeutic strategy below)
 - Loop diuretic by IV bolus, then
 - Loop diuretic by continuous IV infusion, then
 - Thiazide diuretic (metolazone) followed 30 minutes later by loop diuretic every 6 hours, then
 - Loop diuretic (furosemide) diluted in salt-poor albumin
- Congestive heart failure (CHF): afterload reduction, preload reduction (diuretics, nitrates), and inotropes if necessary (see Congestive Heart Failure and Systolic Dysfunction in Chapter 1)
- Cirrhosis: may require IV fluid/colloid challenge in setting of ARF even if total body volume overloaded before initiation of diuretics

Intrinsic ARF

- Caused by damage to tubules, glomeruli, interstitium, and vasculature

Acute Tubular Necrosis⁹

- Most common cause of intrinsic renal insufficiency in hospitalized (38%) and ICU (76%) patients
- Etiologies include ischemia (most frequent), medications, sepsis, pigment (hemoglobin, myoglobin), radiocontrast dye, urate nephropathy (tumor lysis), myeloma, and prolonged prerenal insufficiency
 - Pigment: positive blood on urine dipstick in the absence of RBCs
 - Tumor lysis: high serum potassium, phosphate, uric acid; urine uric acid to urine creatinine ratio >0.7
 - Myeloma: negative protein on urine dipstick, M-spike on serum protein electrophoresis (SPEP)/urine protein electrophoresis (UPEP)

Laboratory Findings

- FeNa $>1\%$
- Urinalysis with pigmented (muddy brown) granular casts observed after centrifugation
- BUN/creatinine ratio $<20:1$
- Hypercalcemia observed in 20%-30% of patients in recovery phase of rhabdomyolysis¹⁰

Treatment

- Treatment is supportive
- Discontinue all potential nephrotoxins
- No proven benefit from diuretics, dopamine, mannitol, atrial natriuretic peptide, or calcium channel blockers¹¹

- N-acetylcysteine may help prevent radiocontrast dye-induced nephropathy in patients with preexisting renal disease¹²
- Limited evidence to suggest that IV fluid alkalinized with sodium bicarbonate may also help to prevent radiocontrast dye-induced nephropathy¹³
- Mannitol may improve outcomes if given early in myoglobinuria¹⁰ but may worsen radiocontrast dye-induced nephropathy¹²
- Alkaline fluid is typically given in rhabdomyolysis but no proven benefit over isotonic saline
- Alkalinize urine in urate nephropathy with goal urine pH of 7.0-7.5
- May see a polyuric phase during recovery of ATN due to excretion of accumulated osmoles (urea) and inefficient sodium reabsorption by immature recovering epithelial cells

Glomerular Disease

- Rare cause of ARF but important to recognize early and treat

Glomerulonephritis (GN)^{14,15}

- Acute GN: characterized by hypertension, oliguria, and azotemia; usually observe < 2 mg/dL increase in creatinine over several weeks
 - Etiology
 - Primary GN: membranoproliferative GN (MPGN), IgA nephropathy, poststreptococcal GN
 - Secondary GN: postinfection MPGN, systemic lupus erythematosus (SLE), any immune complex disorder
 - History: assess for symptoms of connective tissue disease (rash, arthralgias), recent infection, risk factors for viral hepatitis or endocarditis, hemoptysis
 - Physical examination: focus on volume status/evidence of primary renal sodium retention

(e.g., hypertension, CHF, pulmonary congestion), assessment of rashes, synovitis, cardiac murmurs, embolic phenomenon

- Laboratory findings
 - Urinalysis with micro: frequently see proteinuria, hematuria; may see dysmorphic RBCs (suggestive of glomerular origin) or RBC casts
 - Other diagnostic laboratory studies as directed by clinical picture: ANA, dsDNA, C3, C4, CH50, ANCA, anti-GBM Ab, ASO titer, anti-DNAse B Ab, hepatitis B and C serologies, RPR, RF, cryoglobulins if RF+
 - Renal biopsy if patient has active urinary sediment (RBCs, white blood cells [WBCs], and casts) without clear etiology
- Treatment
 - Generally includes measures to control blood pressure (BP) and maintain euvolemia
 - Depending on etiology, immunosuppressive therapy and/or plasma exchange may be indicated based on the specific diagnosis, severity of disease, and presence of salvageable nephrons
- Rapidly progressive GN (RPGN): not a specific pathophysiological entity but a clinical/histological scenario characterized by acute deterioration of renal function due to glomerular injury; usually observe >2 mg/dL increase in creatinine over several weeks
 - Treatment as with any acute GN

DISEASES THAT CAN CAUSE RPGN AND THEIR ASSOCIATED LABORATORY FINDINGS

Disease	Laboratory Finding
Wegener's granulomatosis and other Pauci immune GN (Churg-Strauss, microscopic polyangiitis, polyarteritis nodosa)	ANCA+
Anti-basement membrane disease and Goodpasture's disease	Anti-GBM Ab ⁺

DISEASES THAT CAN CAUSE RPGN AND THEIR ASSOCIATED LABORATORY FINDINGS *(Continued)*

Disease	Laboratory Finding
Poststreptococcal GN	Elevated ASO titers, low C3, nl C4 Anti-DNAse B Ab ⁺
SLE	ANA+, dsDNA+, low C3
Endocarditis	+ blood cultures, low C3, low C4
IgA nephropathy	+/- elevated IgA, normal complement levels
Cryoglobulinemia	Elevated RF, +cryoglobulins, low C3, low C4

- Some specific causes of GN
 - Postinfectious GN
 - Occurs 10-14 days after infection, most commonly with group A streptococcus
 - Other causes include cytomegalovirus, hepatitis B, HIV, Epstein-Barr virus, malaria, toxoplasmosis, and coccidiomycosis
 - Treatment is supportive; no role for steroids
 - IgA nephropathy¹⁷
 - Most common cause of GN in the world
 - Frequently presents with gross hematuria
 - Exacerbated by mucosal infection
 - Elevated IgA in 30%-50% of cases (neither specific nor sensitive)
 - 30%-50% will progress to nephritic syndrome
 - Treatment: Prednisone (60 mg/d for 6 weeks): induces remission in some patients (used primarily for patients with rapid deterioration and active histology); fish oil (12 g/d)—may retard progression of nephropathy; ACE inhibitors; if RPGN, consider steroids + cyclophosphamide, ± plasma exchange

- Henoch-Schonlein purpura (IgA nephropathy with systemic vasculitis)^{16,17}
 - Leukocytoclastic vasculitis that presents with arthralgias, abdominal pain, purpura, nausea, vomiting, melena, azotemia
 - Renal biopsy identical to IgA nephropathy
- Glomerular basement membrane (GBM) disease:
 - GBM renal disease + pulmonary hemorrhage = Goodpasture's disease
 - Bimodal age distribution: young male smokers and women in sixth and seventh decade
 - Often presents with acute oliguria/anuria or hematuria
 - Specific serum antibody against type IV collagen (anti-GBM Ab)
 - 30% will be ANCA +
 - Biopsy reveals linear staining for anti-GBM Ab
 - Treatment: plasmapheresis daily until Ab no longer detected; prednisone and cyclophosphamide for at least 3 months; maintenance cytotoxic therapy; prognosis with early treatment: 85% overall survival, 60% renal survival
- Pauci-immune GN: renal biopsy will not stain for immune complexes^{15,16,18}
 - Wegener's granulomatosis (c-ANCA, proteinase 3 Ab)
 - Churg-Strauss syndrome (p-ANCA, MPO)
 - Microscopic polyangiitis (p-ANCA, MPO)
 - Drug-induced ANCA-associated GN (e.g., hydralazine, penicillamine, propylthiouracil)
 - Typically seen in fifth to seventh decades; slight male predominance
 - Variable clinical picture: fever, arthralgias, weight loss, malaise, purpura, hematuria, upper/lower respiratory tract symptoms, mononeuritis multiplex
 - Treatment: induction IV corticosteroids followed by oral steroids; cyclophosphamide; possible role for plasma exchange and intravenous immunoglobulin in

acute setting with severe symptoms; maintenance cytotoxic therapy

- **Membranoproliferative GN**
 - Both nephritic and nephrotic presentation
 - MPGN type I: immune complex formation and glomerular deposition with classical complement pathway activation
 - MPGN type II: dense deposit disease with alternative complement pathway activation
 - MPGN type III: similar to type I, poorly understood
 - Other etiologies: hepatitis C, mixed cryoglobulinemia, HIV, hepatitis B, bacterial endocarditis, idiopathic
 - Laboratory findings: MPGN type I: low C3, low C4, low CH₅₀; MPGN type II: low C3, normal C4, low CH₅₀, C3 nephritic factor+; endocarditis: positive blood cultures; cryoglobulinemia: RF+, cryoglobulin+; idiopathic: C4 nephritic factor+
 - Treatment: supportive: control BP and limit proteinuria with ACE inhibitors or ARBs; steroids ± cytotoxic agents in RPGN; treat associated disease process if identified
- **SLE nephritis**¹⁹
 - Renal manifestations include both nephritic and nephrotic presentation
 - Presentation includes hematuria, proteinuria, oliguria, hypertension, and azotemia
 - Laboratory findings: ANA, anti-dsDNA Ab; low C3, low C4, low CH₅₀ in proliferative disease
 - Treatment depends on biopsy/histology findings: WHO classification—I. Normal: no specific treatment; II. Mesangial disease: no specific treatment unless disease progression; III. Focal proliferative: induction with corticosteroids and cytotoxic agent, followed by steroid/cytotoxic agent maintenance therapy; IV. Diffuse proliferative: induction with corticosteroids and cytotoxic agent, followed by steroid/cytotoxic agent maintenance therapy; V. Membranous: steroids ± cytotoxic agent

Nephrotic Syndrome²⁰

- Caused by excessive leak of proteins through the glomerular membrane
- Defined by proteinuria (>3.5 g/d), hypoalbuminemia (<3.5 mg/dL), edema, hypercholesterolemia, and lipiduria (oval fat bodies seen on urinalysis)
- Etiology
 - Primary renal disease: minimal change disease, focal segmental glomerulosclerosis (FSGS), membranous GN
 - Secondary renal disease: minimal change disease, FSGS, membranous GN, membranoproliferative GN, SLE, amyloidosis, diabetes mellitus
- Laboratory findings (as indicated by clinical picture): ANA, dsDNA, C3, C4, CH₅₀, SPEP, UPEP, RPR, hepatitis B and C serologies, HIV, ASO, RF
- Treatment
 - Restrict diet with low salt and low cholesterol; ensure adequate protein intake due to risk of wasting
 - Diuretics for edema and hypertension
 - ACE inhibitors or ARBs to limit proteinuria
 - Treat hyperlipidemia
 - No proven benefit for prophylactic anticoagulation
 - Consider immunosuppression for significant/resistant proteinuria
 - Some specific causes of the nephrotic syndrome:
 - Minimal change disease—most common cause of nephrotic syndrome in children; associated with medications (NSAIDs, lithium, interferon) and Hodgkin's lymphoma; biopsy reveals podocyte effacement on electron microscopy; treat with prednisone (1 mg/kg/d) for 4-6 weeks, cytotoxic agents for relapses or steroid-resistant disease
 - Membranous GN: most common cause of primary renal nephrotic syndrome in adults; associated with hepatitis B, solid-tumor malignancy, syphilis, class V

lupus, gold therapy; treatment is generally supportive and includes therapy for underlying disease process if present, steroids + cytotoxic agents have shown some benefit in select cases

- FSGS: idiopathic (most common in the African American population) and associated with HIV, heroin abuse, sickle cell disease, obesity, bisphosphonate therapy
- HIV-associated nephropathy (HIVAN): collapsing variant of FSGS; unlike primary FSGS, kidneys are normal-to-enlarged on ultrasound, patients are less commonly hypertensive, and renal function tends to deteriorate more rapidly; treatment with steroids $\pm$ cytotoxic agents for primary disease, highly active antiretroviral therapy for HIVAN

Acute Interstitial Nephritis^{21,22}

Etiology

- Allergic reaction to medication (most common): beta-lactam antibiotics, sulfa drugs, NSAIDs, diuretics, rifampin
- Infiltrative disease: sarcoid, lymphoma, Sjögren's syndrome, infections (CMV, Rocky Mountain spotted fever, histoplasmosis, legionella, leptospirosis)
- Pyelonephritis

History and Physical Examination

- Fever, papillary rash usually 7-10 days after the initiation of medication in allergic causes
- Fever and costovertebral angle tenderness in pyelonephritis

Laboratory Findings

- Peripheral eosinophilia and eosinophiluria in allergic nephritis
- WBC and WBC casts in urine with positive urine cultures in pyelonephritis

- May observe low-grade proteinuria
- Hyperkalemia early due to collecting duct dysfunction
- May see any type of renal tubular acidosis

Treatment

- Treat underlying disorder
- In allergic reactions, remove the offending agent
- Consider steroids for severe cases

Vascular Disease^{23,24}

- Characterized by endothelial damage leading to occlusion of small, medium, or large renal blood vessels
- Etiologies include thrombotic microangiopathies (thrombotic thrombocytopenic purpura/hemolytic uremic syndrome), malignant accelerated hypertension, systemic vasculitis, atheroemboli, sickle cell disease, scleroderma renal crisis, renal artery or vein occlusion
- Treatment
 - Treat underlying disorder
 - Plasma exchange for the thrombotic microangiopathies
 - IV antihypertensives for malignant accelerated hypertension
 - ACE inhibition in scleroderma renal crisis²⁴

Postrenal Insufficiency^{1,2,4,25}

- Defined as the inability to excrete urine after it is formed

- Results in <5% of all ARF cases
- Etiologies include urethral stricture, BPH, prostate cancer, bladder dysfunction, crystalluria, bilateral kidney stones, retroperitoneal fibrosis, and malignancy

History

- Acute anuria is suggestive of obstruction, although normal voiding does not exclude this diagnosis
- Evaluate for symptoms of BPH and nephrolithiasis

Physical Examination

- Should include prostate examination; evaluation of postvoid residual >200-250 cc indicates obstruction

Diagnostic Studies and Laboratory Evaluation

- Urinalysis with microscopy: may see normal RBC in nephrolithiasis and malignancy; crystals may be present
- May see low FeNa in early obstruction
- Renal ultrasound: 80%-85% sensitive²⁵; false-negatives seen with volume depletion, rapid development of obstruction, and when associated with retroperitoneal fibrosis

Treatment

- Foley catheter placement may temporarily relieve distal obstruction
- Depending on etiology, may require nephrostomy tube placement
- Obstruction with fever or leukocytosis requires emergent drainage
- May see postobstructive diuresis due to osmotic diuresis associated with accumulated solutes (urea): maintain euvolemia with isotonic fluids as necessary



Patient Care Warnings

- Remember that in early glomerulonephritis and early renal obstruction there may be a FeNa of $<1\%$
- Limit the use of heparin in acute glomerular basement membrane disease as pulmonary hemorrhage is a major cause of mortality
- If an SLE patient presents with acute renal failure with an active urinary sediment or low complement levels, the patient almost certainly has proliferative disease, and treatment should begin before or without a renal biopsy

References

- ③ 1. Thadhani R, Pascual M, Bonventre J. Acute renal failure. *N Engl J Med* 1996;334:1448-60.
- ③ 2. Klahr S, Miller S. Acute oligouria. *N Engl J Med* 1998;338:671-75.
- ② 3. Liano F, Pascual J. Epidemiology of acute renal failure: A prospective, multicenter, community-based study. *Kidney Int* 1996;50:811-18.
- ③ 4. Nolan CR, Anderson RJ. Hospital-acquired acute renal failure. *J Am Soc Nephrol* 1998;9:710-18.
- ③ 5. Nissenson AR. Acute renal failure: Definition and pathogenesis. *Kidney Int* 1998;66(Suppl):S7.
- ③ 6. Star R. Treatment of acute renal failure. *Kidney Int* 1998;54:1817-31.
- ③ 7. Blantz RC. Pathophysiology of pre-renal azotemia. *Kidney Int* 1998;53:512-23.
- ③ 8. Lamiere NH, De Vriese AS, Vanholder R. Prevention and non-dialytic treatment of acute renal failure. *Curr Opin Crit Care* 2003;9:481-90.
- ③ 9. Esson ML, Schrier RW. Diagnosis and treatment in acute tubular necrosis. *Ann Intern Med* 2002;137:744-52.
- ③ 10. Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int* 1996;45:413-26.
- ③ 11. Gambaro G, Bertaglia G, Puma G, D'Angelo A. Diuretics and dopamine for the prevention and treatment of acute renal failure: A critical reappraisal. *J Nephrol* 2002;15:213-19.

- ③ 12. Asif A, Epstein M. Prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 2004;44:12-24.
- ① 13. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast induced nephropathy with sodium bicarbonate: A randomized controlled trial. *J Am Med Assoc* 2004;291:2328-34.
- ③ 14. Couser WB. Pathogenesis of glomerular damage in glomerulonephritis. *Nephrol Dial Transplant* 1998;13(Suppl):10-15.
- ③ 15. Hricic DE, Chung-Park M, Sedor J. Glomerulonephritis. *N Engl J Med* 1998;339:888-99.
- ③ 16. Langford C, Balow J. New insights into the immunopathogenesis and treatment of small vessel vasculitis of the kidney. *Curr Opin Nephrol Hyperten* 2003;12:67-72.
- ③ 17. Donadio JV, Grande JP. IgA nephropathy. *N Engl J Med* 2002;347:738.
- ③ 18. Cunard R, Kelly C. Immune-mediated renal disease. *J Allergy Clin Immunol* 2003;111:S637-44.
- ③ 19. Contreras G, Roth D, Pardo V, et al. Lupus nephritis: A clinical review for practicing nephrologists. *Clin Nephrol* 2002;57:95.
- ③ 20. Ponticelli C, Passerini P, Como G, et al. Primary nephrotic syndrome in the elderly. *Contrib Nephrol* 1993;105:33-37.
- ③ 21. Cameron JS. Allergic interstitial nephritis: Clinical features and pathogenesis. *Q J Med* 1988;66:97-115.
- ③ 22. Michel DM, Kelly CJ. Allergic interstitial nephritis. *J Am Soc Nephrol* 1998;9:506.
- ③ 23. Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002;347:589-600.
- ② 24. Steen VD, Constantino JP, Shapiro AP, et al. Outcome in renal crisis in systemic sclerosis: Relation to angiotensin converting enzyme inhibitors. *Ann Intern Med* 1991;114:249-50.
- ③ 25. Webb JA. Ultrasonography in the diagnosis of renal obstruction. *Br Med J* 1990;11:87-90.

OVERVIEW AND INDICATIONS FOR RENAL REPLACEMENT THERAPY

Terminology¹

Hemodialysis

- Transport process that requires passive diffusion of solutes down their concentration gradients
- Dialysate flows countercurrent to blood
- Results in reduction in blood urea nitrogen (BUN) and Cr, increase in Ca^{2+} and HCO_3^-

Hemofiltration

- Transport process that induces filtration (or convection) of plasma/water across the membrane of a hemofilter
- Removal of small and medium molecular-weight solutes (<5000 D)
- Usually results in mild changes in BUN and electrolyte concentrations, depending on the composition of the replacement fluid
- Replacement fluid is required to achieve adequate fluid balance

Hemodiafiltration

- Combination of above two processes
- Solute loss primarily by dialysis but $>25\%$ can be by hemofiltration

Arteriovenous

- An arterial catheter allows blood to flow into the extracorporeal circuit using systemic blood pressure
- No extracorporeal blood pump involved
- Requires arterial puncture
- Unreliable blood flow if hypotension or severe peripheral vascular disease

Venovenous

- No arterial access necessary
- Less systemic anticoagulation
- One dual lumen catheter used
- Requires an extracorporeal blood pump

Modes of Renal Replacement Therapy

- Intermittent hemodialysis (IHD): transports solutes passively down their concentration gradients using a dialyzer membrane

- Hemoperfusion (HP): passage of anticoagulated blood through a device, usually a column, that contains adsorbent particles
- Continuous arteriovenous hemofiltration (CAVH): removes solutes slowly by convection
- Slow continuous ultrafiltration (SCUF): dehydrating procedure with minimal solute clearance
- Continuous arteriovenous hemodialysis (CAVHD): more solute removal than CAVH or SCUF but less fluid removal
- Continuous venovenous hemodialysis (CVVHD): similar to CAVHD but requires blood pump; most common continuous renal replacement therapy (RRT) used
- Continuous arteriovenous hemodiafiltration (CAVHDF): combines diffusion and convection to remove solute, but requires replacement fluid
- Continuous venovenous hemodiafiltration (CVVHDF): similar to CAVHDF but requires blood pump

Accepted Indications for RRT

- Hyperkalemia refractory to the following medical therapy:
 - Insulin glucose (50 mL of a 50% glucose solution as a bolus + 10 units regular insulin)
 - Sodium bicarbonate (50 mEq or 1 amp of a 7.5% solution intravenous (IV) infusion over 5 minutes)
 - Kayexelate (20-30 g with 100 mL of a 20% sorbitol solution to prevent constipation)
 - Beta-2 adrenergic agonists (albuterol 10-20 mg in 4 mL of saline by nasal inhalation over 10 minutes or 0.5 mg by IV infusion or epinephrine 0.05 µg/kg per minute by IV infusion)
 - Calcium gluconate (10 mL of 10% solution or 1 amp IV infused slowly over 2-3 min; stabilizes cardiac membranes)

- Acidemia refractory to medical therapy with sodium bicarbonate infusion ($\text{pH} < 7.20$)
 - Most common cause is persistent hypotension/hypoperfusion (from sepsis, hypovolemia, severe congestive heart failure, etc.) with ongoing lactic acidosis
- Volume overload refractory to medical therapy with high-dose diuretics
 - Most commonly accompanied by persistent hypoxemia secondary to pulmonary edema
- Uremic signs and symptoms (most serious):
 - Pericarditis (electrocardiogram with diffuse ST elevations and PR depressions)
 - Bleeding diathesis (secondary to platelet dysfunction)
 - Encephalopathy manifested by seizures or coma (may also be secondary to severe hyponatremia)
 - Neuropathy
- Ingestions (with serum toxic levels in parentheses):
 - Lithium (2.5-3.5 mg/dL)
 - Theophylline (30-40 mg/dL)
 - Salicylates (80 mg/dL)
 - Alcohols: ethanol, isopropanol (400 mg/dL), acetone, methanol (50-100 mg/dL), ethylene glycol (20 mg/dL)
 - Phenobarbital (10 mg/dL)

Other Possible Indications for RRT

- Hypercatabolic patients requiring aggressive nutritional support
 - 4.4 dialysis sessions/week are required to maintain a BUN of 60 mg/dL in a 50-kg hypercatabolic, critically ill patient; daily sessions are required in a similar 90-kg patient²

- Septic patients with acute renal failure in order to facilitate removal of harmful immunomodulatory substances
 - Small animal studies have shown improvement in left ventricular contractility after CAVH³
 - However, other human studies have shown no change in serum cytokine and complement factor levels despite their removal with hemofiltration⁴

Specific Indications for Different Modes of RRT⁵

- IHD: uremia, drug-induced overdose or nephrotoxicity, hyperkalemia
- HP: drug overdose (theophylline, barbiturates)
- CAVH or SCUF: volume overload
- CVVH: sepsis, acute respiratory distress syndrome (ARDS), burns
- CAVHD or CVVHD: hepatorenal syndrome, sepsis, ARDS
- CAVHDF or CVVHDF: burns, sepsis, ARDS

References

- ③ 1. Golper TA. Continuous renal replacement therapies: Overview. www.uptodate.com
- ② 2. Clark WR, Mueller BA, Kraus MA, et al. Extracorporeal therapy requirements for patients with acute renal failure. *J Am Soc Nephrol* 1997;8:804-12.
- ② 3. Gomez A, Wang R, Unruh H, et al. Hemofiltration reverses left ventricular dysfunction in sepsis in dogs. *Anesthesiology* 1990;73:671-85.
- ② 4. Hoffmann JN, Hartl WH, Deppisch R, et al. Hemofiltration in human sepsis: Evidence for elimination of immunomodulatory substances. *Kidney Int* 1995;48:1563-70.
- ③ 5. Conger J. Dialysis and related therapies. *Semin Nephrol* 1998; 18:533-40.

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GASTROENTEROLOGY

UPPER GI BLEEDING

Definitions, Etiology, and Epidemiology

- Upper gastrointestinal (GI) bleeding: GI bleeding from a source proximal to the ligament of Treitz
- Lower GI bleeding: GI bleeding from a source distal to the ligament of Treitz
- Overall mortality rate of 10% in all patients with upper GI bleeding^{1,2}
- Differential diagnosis includes¹:
 - Peptic ulcer disease (PUD): 55%
 - Esophageal varices: 14%
 - Arteriovenous malformations: 6%
 - Mallory-Weiss tears: 5%
 - Tumors and erosions: 4% each
 - Dieulafoy's lesion: 1%
 - Other: 11%

Causes	Examples
Ulcerative/ erosive	PUD, idiopathic, drug-induced (nonsteroidal anti-inflammatory drugs [NSAIDs]), infectious, stress induced ulcers, Zollinger-Ellison syndrome, esophagitis
Portal hyper- tension	Esophageal varices, gastric varices, duodenal varices, portal hypertensive gastropathy
Structural/ vascular	Arteriovenous malformations (AVMs), idiopathic AVMs, Osler-Weber-Rendu syndrome, Dieulafoy's lesions, watermelon stomach, radiation-induced telangiectasia, blue rubber bleb nevus
Trauma/ surgical	Mallory-Weiss tears, foreign body ingestion, postsurgical anastomoses, fistulas (aortoenteric)

(Continued on following page)

Causes	Examples
Malignancy	Lymphoma, leiomyoma, lipoma, polyps, Kaposi's sarcoma, carcinoid, melanoma, metastatic disease, etc.
Infectious	Esophagitis (<i>Candida</i> , herpes, cytomegalovirus), <i>Helicobacter pylori</i> -induced ulcerations
Medications	Alendronate, tetracycline, KCl, acetylsalicylic acid, NSAIDs, quinidine

Pearls of the History and Physical Examination¹⁻³

History

- Medicine use (NSAIDs, etc.)
- Liver disease, alcohol use
- Previous GI bleeding or endoscopy
- Bleeding disorders (thrombocytopenia, coagulopathy, etc.)
- Wretching (Mallory-Weiss tear)
- Previous surgery or radiation therapy
- Cancer, weight loss, early satiety

Physical Examination

- Hemodynamic assessment
 - Orthostatic symptoms
 - Tachycardia (early and sensitive sign of volume depletion)
- Nasogastric lavage
 - Do until clear; inability to clear is indicative of active bleeding
 - "Coffee grounds" suggest blood has had time to be exposed to gastric acid
- Rectal examination/stool guaiac (estimates of blood)
 - Hemetemesia positive: 5 cc
 - Melena: 50 cc
 - Hematochezia: 500 cc

- Abdominal examination for masses, enlarged liver and spleen, stigmata of liver disease

Diagnostic Studies and Laboratory Values

- Serial monitoring of hemoglobin and hematocrit levels: not a good reflection of blood loss during an acute bleed, but they will fall over time
- Type and cross for blood products
- Platelet count
- Coagulation studies

Guide to Acute Management

RISK STRATIFICATION		
Risk Category	Characteristics	Triage
Very low	Normal hemodynamic levels, no evidence of overt bleeding within 48 hours, normal laboratory results	Outpatient evaluation Follow-up in 1 week
Low	Hemodynamic levels normal within 1 hour of resuscitation; no evidence of active bleeding; no history of liver disease, cardiac disease, or medical comorbidities	Transfer to endoscopy unit if possible for immediate endoscopy
Moderate	Isolated tachycardia that does not resolve despite resuscitation; requires more than two units packed red blood cells, medical comorbidities (liver, cardiac, social)	Stabilize patient Early esophagogastroduodenoscopy (EGD)
High	Evidence of active bleeding, cirrhosis with hematemesis (active hematemesis + beta-receptor blockade in nitroglycerin), persistent hypotension; severe comorbidities, requiring intensive care unit (ICU) stabilization, intubation for airway protection	Admit ICU Endoscopy after stabilization

Hemodynamics¹⁻³

- Patient should be given nothing by mouth
- Monitor hemoglobin or hematocrit levels every 6-8 hours
- Monitor urine output as an assessment of volume status
- Place two large-bore peripheral IVs for blood products; if central access required, largebore Cordis (rather than triple lumen catheter) preferred
- Volume resuscitation
 - Initially with crystalloid IV fluid (normal saline or lactated Ringer's solution)
 - Transfuse blood with goal hemocrit level of 30
- Correct coagulopathy
 - Transfuse fresh frozen plasma for goal international normalized ratio <1.3-1.5
 - Transfuse platelets for counts <50,000

Medical and Mechanical Therapy

Etiology of Bleeding	Therapeutic Options
PUD	IV proton pump inhibitors: pantoprazole <i>H. pylori</i> (dual, triple, quadruple) therapy
Esophageal varices	Octreotide Endoscopic band ligation or sclerotherapy Sengstaken-Blakemore tube for balloon tamponade Embolization Transjugular intrahepatic portosystemic shunt (TIPS)
Angiodysplasia	Endoscopic injection/sclerosing
Mallory-Weiss tears	Usually stops spontaneously without specific intervention
Esophagitis/gastritis	Proton pump inhibitors H ₂ blockers, coating agents (less efficacious)

- Medications
 - Erythromycin 250 mg IV bolus 30-90 minutes prior to endoscopy^{4,5}
 - Promotes gastric emptying for better visualization
 - Improves EGD time and need for repeat endoscopy
 - Octreotide
 - Long-acting analogue of somatostatin to reduce splanchnic blood flow, inhibit gastric acid secretion
 - PUD: relative risk reduction in bleeding of 0.5 with somatostatin⁶; use of octreotide (bolus 50-100 μ g IV followed by 50 μ g/hr $\times$ 3-5 days) less evidence but can be used
 - Esophageal varices: octreotide dose of 50 μ g IV bolus followed by 50 μ g/hr $\times$ 3-5 days revealed improved survival at 5 days⁷
 - Proton pump inhibitors (PPI)¹⁻³
 - Significantly reduces the number of rebleeding events in patients with high risk ulcer lesions
 - Use 80 mg bolus of IV pantoprazole followed by 8 mg/hr infusion; if no rebleeding within 24 hours, may switch to oral PPI (e.g., pantoprazole 40 mg/d or omeprazole 20 mg/d)⁸⁻¹⁰
 - H₂ blockers¹¹
 - Meta-analysis showed no benefit with duodenal ulcer bleeding; small benefit with gastric ulcer bleeding
- Mechanical therapy
 - Endoscopy
 - Diagnostic: identifies source of bleeding and can assess risk of rebleeding
 - Therapeutic: variceal banding, thermal contact, epinephrine injection
 - Complications: aspiration, worsened bleeding, perforation
 - Balloon tamponade
 - Indicated in uncontrolled variceal bleeding or recurrent hemorrhage despite sclerotherapy or banding
 - Must provide airway protection with endotracheal intubation

- Mesenteric arteriography with embolization
 - May be necessary if unable to control bleeding endoscopically
- TIPS
 - Used for refractory variceal hemorrhage despite endoscopy in patients who are poor surgical candidates
 - For high-risk patients, survival at 30 days may be increased from 10%-20% up to 63%¹²
- Surgery
 - Necessary for hemodynamic instability despite vigorous resuscitation or recurrent hemorrhage after initial stabilization



Patient Care Warnings

- ICU monitoring indicated for patients who are hemodynamically unstable, with evidence of continued bleeding (unable to clear nasogastric lavage), with hemocrit drop >6%, or with orthostatic symptoms despite early resuscitation
- All patients should have the equivalent of two working large-bore IVs for volume resuscitation
- In PUD, the risk of rebleeding (least to highest) as determined by endoscopy is: clean based ulcer → oozing without visible vessel → adherent clot → active bleeding

References

- ③ 1. Yacyszyn BR, Thomson AB. Critical review of acid suppression in nonvariceal, acute, upper gastrointestinal bleeding. *Dig Dis* 2000;18:117-28.
- ③ 2. Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: A population-based study. *Am J Gastroenterol* 1995;90:206.

- ③ 3. Jutabha R, Jensen DM. Management of upper gastrointestinal bleeding in the patient with chronic liver disease. *Med Clin North Am* 1996;80:1035-68.
- ③ 4. Frossard JL, Spahr L, Queneau PE, et al. Erythromycin intravenous bolus infusion in acute upper gastrointestinal bleeding: A randomized, controlled, double-blind trial. *Gastroenterology* 2002;123:17-23.
- ① 5. Cofin B, Pocard M, Panis Y, et al. Erythromycin improves the quality of EGD in patients with acute upper GI bleeding: A randomized controlled study. *Gastrointest Endosc* 2002; 56:174-79.
- ① 6. Imperiale TF, Birgisson S. Somatostatin or octreotide compared with H₂ antagonist and placebo in the management of acute nonvariceal upper gastrointestinal hemorrhage: A meta-analysis. *Ann Intern Med* 1997;127:1062-71.
- ① 7. Sung JJ, Chung SC, Yung MY, et al. Prospective randomized study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet* 1995;346:1666-69.
- ① 8. Gisbert JP, Gonzalez L, Calvet X, et al. Proton pump inhibitors versus H₂-antagonists: A meta-analysis of their efficacy in treating bleeding peptic ulcer. *Aliment Pharmacol Ther* 2001;15:917.
- ① 9. Kaviani MJ, et al. Effect of oral omeprazole in reducing rebleeding in bleeding peptic ulcers: A prospective, double-blind, randomized, clinical trial. *Aliment Pharmacol Ther* 2003;17:211.
- ① 10. Lau JY, Sung JJ, Lee KK, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *New Engl J Med* 2000;343:310.
- ① 11. Levine JE, Leontiadis GI, Sharma VK, et al. Meta-analysis: The efficacy of intravenous H₂-receptor antagonists in bleeding peptic ulcer. *Aliment Pharmacol Ther* 2002;16:1137.
- ③ 12. La Berge JM, Ring EJ, Gordon RL, et al. Creation of trans-jugular intrahepatic portosystemic shunts with the Wallstent endoprosthesis: Results in 100 patients. *Radiology* 1993; 187:413.

LOWER GI BLEEDING

Definitions, Etiology, and Epidemiology

- Lower gastrointestinal (GI) bleeding: GI bleeding from a source distal to the ligament of Treitz; there are three classifications:
 - Acute lower GI bleed: bleeding <3 days' duration

resulting in hemodynamic compromise, anemia, or need for blood transfusion

- Intermittent melena/hematochezia: chronic GI bleeding lasting for >3 days
- Obscure GI bleeding: positive fecal occult blood test or iron-deficiency anemia with no obvious source of GI blood loss and bleeding of unknown origin that persists or recurs despite (-) upper GI endoscopy or colonoscopy¹
- Overall mortality rate of 4%-21%² (depending on age >60 years), multiple medical comorbidities, transfusion requirements in excess of 5 units, need for operation, and other recent physiological stress)
- 20-27/100,000 annual incidence, males more affected than females, and 200-fold increase between the third and ninth decades of life³
- Spontaneous remission rate of 80% (same as in upper GI bleeding)⁴

Differential Diagnoses³⁻⁸

- Upper GI tract (10%)
- Small intestine (5%: neoplasm, Crohn's disease, aortoenteric fistula, angiodysplasia, Meckel's diverticulum)
- Diverticular bleeding (42%-55%)
 - Increased risk with nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin
 - 60%-80% bleeding diverticula are in right colon (but 90% of all diverticula are in the left colon)
 - Bleeding spontaneously ceases in 75%, recurs in 38% of cases
 - Recurrence is 9% at 1 year and 25% at 4 years
- Angiodysplasia (3%-12%)
- Tumor (2%-26%)
- Inflammatory bowel disease (10%)
- Ischemic colitis (9%)
 - Seen in patients with vascular disease or risk factors
 - May be foretold by prior hypotensive event

- Internal hemorrhoid (<10%)
- Undiagnosed (10%)
- Postpolypectomy bleeding (4%)
 - Associated with restarting NSAID or aspirin too quickly
- Rectal ulcer (hard stool-induced pressure ulcers)
- Acute infectious colitis
- Pseudomembranous colitis
- Graft-versus-host disease (recent transplant recipient)
- Dieulafoy's lesion (exposed submucosal vessel) of the colon
- Radiation colitis
 - May be delayed 3 years after radiation therapy
- Aortoenteric fistula (aortic graft-enteric fistula)
 - Occurs in those with aortic surgery history
 - Requires immediate emergency management

Pearls of the History and Physical Examination

History

- Age of patient⁵
- Nature and duration of bleeding
- Stool color and frequency
- Associated symptoms: abdominal pain, recent change in bowel movement, fever, urgency/tenesmus, weight loss
- Previous lower GI bleeding, trauma, past abdominal surgeries, peptic ulcer disease, inflammatory bowel disease, x-ray therapy to abdomen/pelvis, colonic diverticulosis, hemorrhoids, lower GI tract surgery
- Cardiopulmonary or liver disease¹
- Medication use (NSAIDs, anticoagulants)
- Renal failure or insufficiency (uremic platelet dysfunction), bleeding disorders (platelets, coagulopathy, etc.)
- Chemotherapy (mucositis) or radiation therapy⁴
- Cancer, unexplained weight loss, or early satiety

Physical Examination

- Vital statistics with assessment of orthostasis
- Nasogastric (NG) lavage (to evaluate for brisk upper GI bleeding source)
- Abdomen (masses, peritoneal signs)
- Digital rectal examination (pain, hematochezia ≈500 cc blood loss, neoplasm)¹

Diagnostic Studies and Laboratory Values

- Complete blood count with serial monitoring of hemoglobin (Hgb) and hematocrit (Hct) levels
- Coagulation studies (correct coagulopathy)
- Type and crossmatch

Guide to Acute Management^{3,8-14}

Initial Steps

- Hemodynamic monitoring and stabilization
- Patient should be given nothing by mouth
- NG aspirate should be bilious and without blood
- Monitor Hgb and Hct levels every 6-8 hours
- Monitor urine output as an assessment of volume status
- Place two large-bore peripheral IV lines for blood products; if central access required, should use large-bore Cordis (rather than triple-lumen catheter)
- Volume resuscitation
 - Initially with crystalloid IV fluid (normal saline or lactated Ringer's solution)
 - Transfuse blood with goal Hct of 30 (to provide adequate reserve if intervention undertaken)
- Correct coagulopathy
 - Transfuse fresh frozen plasma for goal international normalized ratio <1.3-1.5
 - Transfuse platelets for counts <50,000

- Upper endoscopy may be necessary to rule out upper tract source
- Anoscopy to evaluate for anorectal lesion (bleeding hemorrhoid)

Colonoscopy

- Has diagnostic and therapeutic applications to the patient who is responding or is not yet refractory to hemodynamic optimization and resuscitation
- Useful to identify bleeding source when brisk bleeding has stopped
- Useful to perform within 6-12 hours of presentation; earlier the colonoscopy is performed, better the diagnostic yield
- May require rapid preparation and purge (2-6 L bowel preparation over 2-4 hours) via nasogastric tube if necessary
- Studies suggest that endoscopic therapy is possible in 30%-40% of lower GI bleeding
 - Arteriovenous malformations: thermal contact therapy
 - Ulcers and postpolypectomy bleeding: thermal contact, epinephrine injection, or metallic clip placement
 - Diverticular hemorrhage: combination of thermal therapy and epinephrine injection
 - Radiation proctitis: argon plasma coagulation

Red Blood Cell (RBC) Nuclear Scintigraphy (Tagged RBC Scan)

- Useful if continued bleeding in:
 - Patient who is responding or is not yet refractory to hemodynamic optimization and resuscitation
 - Patient being prepared for colonoscopy
- Can localize a site with a bleeding rate as low as 0.1 cc/min (patient bleeding at this rate requires 1 unit of packed RBCs every 2-4 hours)

- Sensitivity five times greater than that of angiogram
- Scans with early positive results (e.g., within 2 hours of image acquisition) are more useful than later positive scans
- If the scan result is negative, colonoscopy should be performed within 6-12 hours
- Tagged study alone does not make diagnosis (e.g., blood seen in the left upper quadrant could be from splenic flexure, stomach, or duodenum)
- Only gives information regarding general region of bleeding
- Not a therapeutic modality; not reliable for directing surgical therapy

Angiography

- More specific but less sensitive than tagged RBC study
- Can localize site with bleeding rate ≈ 0.5 -1 cc/min (1 unit per hour transfusion requirement)
- Therapeutic modality via embolization or vasoconstrictor administration
 - Bleeding site seen on colonoscopy but cannot be treated
 - Patient is suboptimal surgical candidate
 - Vasopressin
 - Requires continuous IV infusion in intensive care unit (ICU)
 - When stopped, rebleed rates as high as 50% occur
 - Complications: fluid retention, hyponatremia, hypertension, arrhythmias, pulmonary edema, cardiac ischemia
 - Embolization
 - Catheter-directed microcoils, gelatin sponge pledgets, or polyvinyl alcohol into target vessel
 - Arrests bleeding in up to 71% of patients
 - Risk of intestinal infarction
 - No controlled trials, so precise role yet to be established

Surgery

- Urgent surgery indicated in patients
 - With persistent shock despite aggressive and appropriate resuscitation
 - When other therapeutic interventions are not feasible or have failed
 - With recurrent or continued bleeding
 - With transfusion >6 units during hospital course or >4 units in 24 hours
- Accurate preoperative localization of bleeding area is key



Patient Care Warnings

- ICU monitoring indicated for patients who are hemodynamically unstable, with evidence of continued bleeding, with advanced age (>60 years) and/or multiple comorbid conditions, or with orthostatic symptoms despite early aggressive resuscitation
- 80% of bleeding resolves on its own so supportive and resuscitative measures are key
- Morbidity and mortality rates higher with older patients and those with more comorbidities
- All patients should have the equivalent of two working large-bore IV lines for volume resuscitation
- Early involvement of appropriate services is key to management

References

- ③ 1. Amarapurkar D, Patel N. Endoscopic management of lower gastrointestinal bleeding. *Bombay Hosp J* 2002;44:15-22.
- ③ 2. Peter DJ, Dougherty JM. Evaluation of the patient with gastrointestinal bleeding: An evidence based approach. *Emerg Med Clin North Am* 1999;17:239-61.

- ② 3. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: A population-based study. *Am J Gastroenterol* 1997; 92: 419-24.
- ③ 4. Manten HD, Green JA. Acute lower gastrointestinal bleeding: A guide to initial management. *Postgrad Med* 1995;97:154-57.
- ③ 5. DeMarkles MP, Murphy JR. Acute lower gastrointestinal bleeding. *Med Clin North Am* 1993;77:1085-1100.
- ③ 6. Fallah MA, Prakash C, Edmundowicz S. Acute gastrointestinal bleeding. *Med Clin North Am* 2000;84:1183-1208.
- ③ 7. Moses S. Lower gastrointestinal bleeding. *Family Practice Notebook*. www.fpnotebook.com
- ③ 8. Lung E. Evaluation and management of gastrointestinal bleeding: Lower and obscure gastrointestinal bleeding. *Advanced Studies Med* 2004;4:245-50.
- ③ 9. Yacyshyn BR, Thomson AB. Critical review of acid suppression in nonvariceal, acute, upper gastrointestinal bleeding. *Dig Dis* 2000;18:117-28.
- ② 10. Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: A population-based study. *Am J Gastroenterol* 1995;90:206-11.
- ③ 11. Jutabha R, Jensen DM. Management of upper gastrointestinal bleeding in the patient with chronic liver disease. *Med Clin North Am* 1996;80:1035-68.
- ③ 12. Voeller GR, Bunch G, Britt LG. Use of technetium-labeled red blood cell scintigraphy in the detection and management of gastrointestinal hemorrhage. *Surgery* 1991;110: 799-804.
- ② 13. Sherman LM, Shenoy SS, Cerra FB. Selective intra-arterial vasopressin: Clinical efficacy and complications. *Ann Surg* 1979;189:298-302.
- ② 14. Peck DJ, McLoughlin RF, Hughson MN, et al. Percutaneous embolotherapy of lower gastrointestinal hemorrhage. *J Vasc Interv Radiol* 1998;9:747-51.

ACUTE LIVER FAILURE

Definitions, Etiology, and Epidemiology

- Acute liver failure (ALF) formerly known as fulminant hepatic failure
- Essential to recognize early and transfer patient to a liver transplant center
 - Altered mentation and coagulopathy (prothrombin

time [PT] >4 seconds, international normalized ratio [INR] >1.5) are grave hallmarks of ALF¹

- Acute and severe liver injury impairing synthetic function and precipitating encephalopathy in an individual thought to have a previously normal liver^{1,2}
 - Defined by timing of onset of disease to onset of encephalopathy
 - Many intervals have been used: hyperacute (7 days or less); acute (7-28 days); subacute (28 days to 6 months)
- Etiologies include:
 - Viral: hepatitis B (leading cause worldwide, 7% in United States), hepatitis A (4%), hepatitis D super- or coinfection, hepatitis E (which may complicate third trimester of pregnancy), Epstein-Barr virus, herpes simplex, and varicella
 - Toxin: acetaminophen (currently comprises 50%), idiosyncratic drugs (12%), mushrooms, and organic solvents
 - Vascular: ischemic hepatitis, Budd-Chiari syndrome, and portal vein thrombosis
 - Metabolic: Reye's syndrome, fatty liver of pregnancy (*hemolysis, elevated liver enzyme levels and a low platelet count* [HELLP]),³ and Wilson's disease
- Viral and acetaminophen lead causes of ALF^{4,5}
- With the exception of pregnancy-induced liver disease and its association with hepatitis E, there is no predilection for race or sex, and age plays a role only in morbidity and mortality (<10 or >40 years of age fare poorly⁶)
- Spontaneous recovery is more likely with lower grades of encephalopathy (grade I-II: 65%-70%; grade III: 40%-50%; grade IV: <20%)⁷ (see section titled Hepatic Encephalopathy for grading)

Pearls of the History and Physical Examination

History

- Question family members and friends (encephalopathy may limit and complicate history)
- Onset of jaundice, encephalopathy, alcohol use, prescription medication use, cocaine,⁸ ecstasy,⁹ herbal or traditional medicine use, family history of liver disease (Wilson's disease), exposure risk factors for viral hepatitis (travel, transfusions, sexual contacts, occupation, body piercing), and toxin ingestion (mushrooms,¹⁰ organic solvents,¹¹ phosphorus in fireworks).

Physical Examination

- Evidence for cerebral edema and increased intracranial pressure (ICP) (decerebrate posturing, papilledema, hypertension, or bradycardia)
- Jaundice
- Kayser-Fleischer rings (Wilson's disease)
- Ascites and anasarca
 - Rapid development of ascites with abdominal pain suggests possibility of hepatic vein thrombosis (Budd-Chiari syndrome)
- Hepatic encephalopathy; sometimes agitation in early stages
- Stigmata of liver disease, track marks, and fetor hepaticus
- Signs of cirrhosis (e.g., spiders) should be absent

Diagnostic Studies and Laboratory Values

Blood Tests¹²

- Complete blood count: in 80% of cases platelets are often low ($<100,000/\text{mm}^3$)
- Serum chemistries: low potassium due to renal

losses; low bicarbonate due to hyperventilation or acidosis; low glucose; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) greater than 500-10,000 units/L; low albumin and total protein (high total protein suggests chronicity or autoimmune hepatitis); low calcium; low phosphate; low magnesium; high bilirubin (>30 mg/dL indicates renal failure or hemolysis—bilirubin may not be high, particularly in acetaminophen cases—these are characterized by very high ALT ≥ 3500); alkaline phosphatase (if low, consider Wilson's disease, if high, consider lymphoma or Budd-Chiari syndrome)

- Coagulation studies: high PT
- Arterial blood gases: high pH (>7.5) due to respiratory alkalosis; if low (<7.3), a bad prognostic sign; low Pco_2 ; low Po_2 is a bad prognostic sign
- Toxicology screen: if positive result for Tylenol (often negative in late presentation cases), see chapter titled Toxidromes
- Hepatitis serologies

Guide to Acute Management

Decision Paradigm

- Hepatic encephalopathy mandates intensive care unit (ICU) admission^{13,14}
- Manage acute complications: encephalopathy, cerebral edema, coagulopathy, acute renal failure, and sepsis
- Contact the nearest liver transplantation facility for transfer, especially if grade I-II hepatic encephalopathy is present; later grades may preclude transfer (patients usually intubated at grade III)¹⁴
- Patient selection for transplantation (meeting criteria endorses urgency for transfer)

THE KING'S COLLEGE LIVER UNIT CRITERIA FOR LIVER TRANSPLANTATION¹⁵

Tylenol-induced hepatic failure¹⁵

- Arterial pH <7.3 (regardless of encephalopathy grade)
- Or all three of following:
 - PT >100 sec
 - Serum creatinine >301 $\mu\text{mol/L}$ (3.4 mg/dL)
 - Grade III/IV encephalopathy

Non-Tylenol-induced hepatic failure¹⁵

- PT >100 sec
- Or any three of following (regardless of encephalopathy grade)
 - Drug-induced, non-A/non-B halothane hepatitis
 - Jaundice > 7 d before encephalopathy
 - Age <10 or >40 years
 - PT > 50 sec
 - Serum bilirubin >308 $\mu\text{mol/L}$ (18 mg/dL)

Contraindications: suspected neurological damage, refractory hypotension, overwhelming sepsis, AIDS, advanced cardiopulmonary disease,¹⁶ alcohol or illicit drug use in the prior 6 months with a diagnosis of substance abuse

Relative contraindications: psychiatric illness, HIV, active substance abuse, portal vein thrombus, hepatopulmonary syndrome with PO_2 <50 mm Hg, cholangiocarcinoma, age >65 years,¹⁶ intrahepatic tumor larger than 5 cm

Antidotes

- Tylenol overdose: refer to the section titled Toxidromes in Chapter 3
- Mushroom poisoning (always associated with cholinergic crisis, sweating, and profuse diarrhea)
 - Immediate goals: gastric lavage, 50 g activated charcoal via nasogastric tube, and electrolyte resuscitation
 - Penicillin^{17,18} 300,000-1,000,000 U/kg/d intravenously in divided doses + sylbinin¹⁸⁻²⁰ 20-50 mg/kg/d
 - Transplantation may be the only option if treatment is initiated 8-10 hours after ingestion¹⁰

Neurological

- Hepatic encephalopathy (see section titled Hepatic Encephalopathy)
- Cerebral edema (75%-80% of patients with grade IV encephalopathy)²¹
 - Presents with Cushing's triad (hypertension, bradycardia, irregular respirations), decerebrate posturing, and epileptiform activity
 - Mechanical ventilation strongly recommended for grade III-IV encephalopathy (respiratory rate 14-18, tidal volume 7 multiplied by the patient's kilogram weight, positive end-expiratory pressure 2-4 mm Hg)¹²
- ICP monitoring
 - Transducers can be placed in epidural, subdural, or parenchymal locations; complication rates are 3.8%, 20%, and 22% respectively; fatal hemorrhage was the lowest in epidural transducers, making them preferable although less accurate²²; no data currently support their use as no improvement in outcomes can be demonstrated with ICP monitoring.
 - Noninvasive monitoring of ICP and cerebral lactate levels with computed tomography (CT), transcranial Doppler, positron emission tomography, and magnetic resonance imaging (MRI) considered ineffective because they are relatively insensitive for monitoring ICP fluctuations²³; CT²⁴ and MRI²⁵ alone also correlate poorly with ICP—only obvious in the most advanced cases: use CT to rule out intracranial hemorrhage; be careful about contrast use due to renal insufficiency
 - Goals are to keep ICP <20 mm Hg and cerebral perfusion pressure (CPP) (which equals mean arterial pressure minus intracranial pressure) >50 mm Hg²⁶
 - Quiet area (minimal sensory stimulation), 30-degree head elevation²⁷ (not 45 degrees as this can reduce CPP), minimal physiotherapy or endotracheal suctioning,¹⁶ avoid benzodiazepine sedation

- If ICP >20 mm Hg, hyperventilation can be instituted; however, this remains controversial and effects are considered short-term^{28,29}
- Mannitol: 0.5-1 g/kg intravenous (IV) bolus to keep osmolality below 320 mOsm/L; repeated as necessary.
- Moderate hypothermia: experimentally investigated successfully in patients refractory to mannitol and ultrafiltration who were cooled to a core temperature of 32°-33°C for a mean of 13 hours as a bridge to transplant³⁰; repeated successfully in a noncontrolled setting with 13 of 14 patients refractory to standard medical therapy, again as a bridge to transplantation³¹; hypothermia will be subjected to a controlled trial but is currently not recommended because it is highly experimental—it is effective, but not yet proved safe
- Thiopental: 10 µg/kg/min barbiturate infusion for intractable intracranial hypertension, with side effects of hypotension that were controlled with dose reduction³²

Coagulopathy

- Failing liver's inability to synthesize clotting factors led commonly to GI ulceration before use of H₂ blockers or, currently, proton pump inhibitors
- Intravenous H₂ blockers: ranitidine 50 mg IV every 8 hours,³³ considered superior to antacids³⁴
- Sucralfate can be given via nasogastric tube (1 g every 6 hours³³) for those intolerant of H₂ blockers
 - Trends favoring sucralfate over H₂ blockers for its antibacterial effects³⁵ and maintenance of gastric acidity and therefore inhibiting growth of gram-negative rods, both of which decrease the risk of aspiration/nosocomial pneumonia³⁶
- The largest trial to date showed lower rate of clinically significant GI bleeding with ranitidine, and no difference between the two in terms of

nosocomial pneumonia, length of ICU stay, or mortality rate³³

- Proton pump inhibitors are also used but are less well studied³⁷
- Fresh frozen plasma (FFP) administration is not indicated in the absence of active bleeding³⁸
- Do not treat elevated INR; use the INR value to help gauge prognosis, unless there is active bleeding
- Anticipation or exacerbation of volume overload, which can increase ICP, can preclude use of FFP; recombinant activated factor VII (rFVIIa) may play a role in such scenarios
 - rFVIIa transiently corrects PT³⁹ in nonbleeding cirrhotic patients undergoing an elective procedure⁴⁰ and acutely controls bleeding in liver failure⁴¹
 - In a nonrandomized setting, rFVIIa in combination with FFP facilitated invasive procedures and improved post-transplant survival in patients meeting King's College criteria with severe coagulopathy in ALF⁴²; rFVIIa has been used successfully in coagulopathy refractory to FFP⁴³
 - There have been no trials defining optimal dosing or safety profiles, and doses have ranged 40-180 µg/kg IV bolus in critical patients^{41,42}

Acute Renal Failure

- Eliminate nephrotoxic drugs
- Renal-dose dopamine is controversial⁴⁴; in hepatorenal syndrome (see section titled Hepatorenal and Hepatopulmonary Syndromes) splanchnic vasoconstrictors are promising⁴⁵; and the use of loop diuretics is controversial¹⁶
- Anuria, acidosis, hyperkalemia, hyponatremia, volume overload, and rising creatinine warrant renal support; continuous venous-venous hemodialysis is preferred⁴⁶

Sepsis

- Infection is very common in ALF patients, usually with gram-positive organisms due to invasive procedures and catheters
- Look for evidence of systemic inflammatory response syndrome, and administer antibiotics if fever, tachycardia, etc., indicate that infection has occurred
- Do not wait for positive blood cultures; prophylactic antibiotics have not been shown to improve survival and are generally not given
- Fungal infections are underrecognized in ALF and, therefore, are ineffectively treated; *Candida albicans* was the chief offender in one series⁴⁷



Patient Care Warnings

- Essential to recognize early and transfer to a liver transplant center
- Transplantation remains the mainstay of treatment for ALF⁴⁸
- Treat hypoglycemia (keep serum glucose >65 mg/dL)⁴⁸

References

1. Trey C, Davidson LS. The management of fulminant hepatic failure. In Popper H, Shaffner F, eds. *Progress in Liver Disease*. New York, Grune and Stratton, 1970:282.
2. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: Definitions and causes. *Semin Liver Dis* 1986;6:97-106.
3. Burroughs AK. Pregnancy and liver disease. *Forum Genova* 1998;8:42-58.
4. Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137:947-54.

- ③ 5. O'Grady JG, Portmann B, Williams R. Fulminant hepatic failure. In Schiff L, Schiff R, eds. *Diseases of the Liver*. Philadelphia, JB Lippincott, 1993.
- ③ 6. White HM. Evaluation and management of liver failure. In Rippe JM, ed. *Intensive Care Medicine*, 3rd ed. Boston, Little Brown, 1996.
- ③ 7. O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439-45.
- ③ 8. Silva MO, Roth D, Reddy KR, et al. Hepatic dysfunction accompanying acute cocaine intoxication. *J Hepatol* 1991;12:312-15.
- ③ 9. Henry JA, Jeffreys KJ, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). *Lancet* 1992;340:384-87.
- ③ 10. Klein AS, Hart J, Brems JJ, et al. Amanita poisoning: treatment and the role of liver transplantation. *Am J Med* 1989;86:187-93.
- ③ 11. Ruprah M, Mant TG, Flanagan RJ. Acute carbon tetrachloride poisoning in 19 patients: Implications for diagnosis and treatment. *Lancet* 1985;1:1027-29.
- ③ 12. Lee WM. Medical management of acute liver failure. In Lee WM, Williams R, eds. *Acute Liver Failure*. Cambridge, United Kingdom, Cambridge University Press, 1997: 117-18.
- ③ 13. Daas M, Plevak DJ, Wijdicks EF, et al. Acute liver failure: Results of a 5-year clinical protocol. *Liver Transplant Surg* 1995;1:210-19.
- ③ 14. Ede RJ, Williams RW. Hepatic encephalopathy and cerebral edema. *Semin Liver Dis* 1986;6:107-18.
- ② 15. O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure: Liver Unit, King's College School of Medicine, London, United Kingdom. *Gastroenterology* 1989;97:439-45.
- ③ 16. Rahman T, Hodgson H. Clinical management of acute hepatic failure. *Intensive Care Med* 2001;27:467-76.
- ③ 17. Floersheim GL, Schneeberger J, Bucher K. Curative potencies of penicillin in experimental *Amanita phalloides* poisoning. *Agents Actions* 1971;2:138-41.
- ③ 18. Floersheim GL, Eberhard M, Tschumi P, et al. Effects of penicillin and silymarin on liver enzymes and blood clotting factors in dogs given a boiled preparation of *Amanita phalloides*. *Toxicol Appl Pharmacol* 1978;46:455-62.
- ③ 19. Antweiler H. Silymarin and polyvinylpyridine-N-oxide as experimental antagonists of the intoxication by *Amanita phalloides* or its single toxins. *Curr Probl Clin Biochem* 1977;7:111-20.
- ③ 20. Hruby K, Csomos G, Fuhrmann M, et al. Chemotherapy of *Amanita phalloides* poisoning with intravenous silibinin. *Hum Toxicol* 1983;2:183-95.

- ③ 21. Lee WM. Acute liver failure. *N Engl J Med* 1993;329:1862-72.
- ③ 22. Blei AT, Olafsson S, Webster S, et al. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet* 1993;341:157-58.
- ③ 23. Shiogai T, Nara I, Saruta K, et al. Continuous monitoring of cerebrospinal fluid acid-base balance and oxygen metabolism in patients with severe head injury: Pathophysiology and treatments for cerebral acidosis and ischemia. *Acta Neurochir Suppl* 1999;75:49-55.
- ③ 24. Munoz SJ, Robinson M, Northrup B, et al. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. *Hepatology* 1991;13:209-12.
- ③ 25. Mukherjee KK, Chhabra R, Khosla VK. Raised intracranial pressure in hepatic encephalopathy. *Indian J Gastroenterol* 2003;22 Suppl 2:S62-65.
- ③ 26. Hoofnagle JH, Carithers RL Jr, Shapiro C, et al. Fulminant hepatic failure: Summary of a workshop. *Hepatology* 1995;21:240-52.
- ① 27. Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. *Crit Care Med* 1993;21:328-38.
- ① 28. Strauss G, Hansen BA, Knudsen GM, et al. Hyperventilation restores cerebral blood flow autoregulation in patients with acute liver failure. *J Hepatol* 1998;28:199-203.
- ① 29. Ede RJ, Gimson AE, Bihari D, et al. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. *J Hepatol* 1986;2:43-51.
- ③ 30. Jalan R, Damink SW, Deutz NE, et al. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet* 1999;354:1164-68.
- ③ 31. Jalan R, Olde Damink SW, Deutz NE, et al. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. *Gastroenterology* 2004;127:1338-46.
- ③ 32. Forbes A, Alexander GJ, O'Grady JG, et al. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. *Hepatology* 1989;10:306-10.
- ① 33. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation: Canadian Critical Care Trials Group. *N Engl J Med* 1998;338:791-97.
- ① 34. Macdougall BR, Bailey RJ, Williams R. H₂-receptor antagonists and antacids in the prevention of acute gastrointestinal haemorrhage in fulminant hepatic failure: Two controlled trials. *Lancet* 1977;1:617-19.

- ③ 35. Tryba M, Mantey-Stiers F. Antibacterial activity of sucralfate in human gastric juice. *Am J Med* 1987;83:125-27.
- ① 36. Driks MR, Craven DE, Celli BR, et al. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers: The role of gastric colonization. *New Engl J Med* 1987;317:1376-82.
- ③ 37. Daley RJ, Rebeck JA, Welage LS, et al. Prevention of stress ulceration: Current trends in critical care. *Crit Care Med* 2004;32:2008-13.
- ① 38. Gazzard BG, Henderson JM, Williams R. Early changes in coagulation following a paracetamol overdose and a controlled trial of fresh frozen plasma therapy. *Gut* 1975;16: 617-20.
- ③ 39. Bernstein DE, Jeffers L, Erhardtson E, et al. Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: A preliminary study. *Gastroenterology* 1997;113:1930-37.
- ① 40. Jeffers L, Chalasani N, Balart L, et al. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology* 2002; 123:118-26.
- ③ 41. Chuansumrit A, Chantarojanasiri T, Isarangkura P, et al. Recombinant activated factor VII in children with acute bleeding resulting from liver failure and disseminated intravascular coagulation. *Blood Coagul Fibrinolysis* 2000;11:S101-105.
- ③ 42. Shami VM, Caldwell SH, Hespenheide EE, et al. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl Surg* 2003;9:138-43.
- ② 43. Brown JB, Emerick KM, Brown DL, et al. Recombinant factor VIIa improves coagulopathy caused by liver failure. *J Pediatr Gastroenterol Nutr* 2003;37:268-72.
- ③ 44. Power DA, Duggan J, Brady HR. Renal-dose (low-dose) dopamine for the treatment of sepsis-related and other forms of acute renal failure: Ineffective and probably dangerous. *Clin Exp Pharmacol Physiol Suppl* 1999;26: S23-28.
- ① 45. Hadengue A, Gadano A, Moreau R, et al. Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. *J Hepatol* 1998;29: 565-70.
- ③ 46. Davenport A, Finn R, Goldsmith HJ. Management of patients with renal failure complicated by cerebral oedema. *Blood Purif* 1989;7:203-09.
- ③ 47. Rolando N, Harvey F, Brahm J, et al. Fungal infection: A common, unrecognised complication of acute liver failure. *J Hepatol* 1991;12:1-9.
- ③ 48. Polson J, Lee WM. AASLD position paper: The management of acute liver failure. *Hepatology* 2005;41:1179-97.

ACUTE MESENTERIC ISCHEMIA

Definitions, Etiology, and Epidemiology

- Sudden onset of decreased blood flow through the intestinal circulation caused by embolus, thrombus, or vasospasm
- Splanchnic blood flow can range 10%-40% of cardiac output
- The celiac artery is rarely involved in acute mesenteric ischemia because its anatomy does not favor embolic obstruction and because of its extensive collateral system
- Superior mesenteric artery (SMA) is the major offender, leading to ischemia of the small intestine and proximal colon¹
- Inferior mesenteric artery (IMA) occlusion causes ischemic colitis, but if occlusion occurs gradually and vascular collaterals are given time to develop, patient may be asymptomatic

ANATOMY²

Artery ^{1,3,4}	Supplies
Celiac	Foregut, hepatobiliary system, spleen
SMA	Small intestine, cecum, ascending colon, proximal midtransverse colon
IMA	Distal transverse colon, descending colon, sigmoid colon, rectum
Collateral circulation	Celiac artery and SMA interconnect through the gastroduodenal and pancreaticoduodenal arteries in foregut; SMA and IMA interconnect via the marginal artery of Drummond and arc of Riolan at splenic flexure Superior hemorrhoidal arteries and IMA interconnect with the inferior hemorrhoidal arteries and iliac arteries

EPIDEMIOLOGY (1:1000 HOSPITAL ADMISSIONS)

Cause	Pathophysiology ^{2,5-8}	Epidemiology ^{4,5,7,8}	Risk Factors ^{3-5,8}	Anatomy ^{1,3,4,6,8,9}
Mesenteric arterial embolus (MAE) (25% of cases) ¹	Total occlusion of artery	Mean age 69 y; range 60-75 y; mortality rate 70%-90%	Valvular disease, cardiac arrhythmia, mural thrombosis, history of thromboembolic events, recent angiography or coronary artery bypass graft, aortic dissection	50% in SMA in distal branches near origin of middle colic artery 15% in origin of SMA
Mesenteric arterial thrombosis (MAT) (50% of cases) ¹	Narrowing of luminal diameter	Mean age 71 y; age range 59-78 y; Mortality rate 70%-90%	Coronary artery disease, peripheral vascular disease, hypertension, aortic dissection, hypercoagulable state, dehydration, abdominal aortic aneurysm repair	Majority at the origin of the SMA
Mesenteric venous thrombosis (MVT) (5% of cases) ¹	Hypercoagulability due to any cause (can be inherited or aquired)	Mean age 70 y; age range 43-74 y; Women > men; Mortality rate 20%-50%	Venous hypercoagulability, polycythemia, cancer, intra-abdominal inflammation, postoperative states, cirrhosis, portal hypertension, oral contraceptives, tobacco use by a patient on oral contraceptives or with an underlying hypercoagulability, abdominal trauma	Majority in superior mesenteric vein
Nonocclusive mesenteric ischemia (20% of cases) ¹	Severe mesenteric vasoconstriction from shock (sepsis, heart failure, or hemorrhage)	Mean age 69 y; age range 59-76 y; Mortality rate 70%-90%	Shock secondary to any cause, bypass surgery, recent use of vasoconstricting medication (digoxin, pressors), sepsis, burns, pancreatitis	Diffuse related to shock and vasoconstriction of mesenteric vessels

Pearls of the History and Physical Examination¹⁰

Intestinal Angina

- History: abdominal pain after meals (usually <3 hours), weight loss, fear of eating (sitophobia)
- Physical examination: evidence of peripheral vascular disease: bruits, decreased peripheral pulses

Mesenteric Arterial Embolus^{1,4,8}

- History: sudden onset of severe, poorly localized periumbilical pain; previous history of emboli or condition predisposing to emboli
- Physical examination
 - Abdomen initially soft; peritoneal signs develop later; bowel sounds may be normal, increased (often early), or decreased
 - Blood in rectum in 16% of cases; occult positive in 25% of cases
 - Atrial fibrillation

Mesenteric Arterial Thrombosis (Superior Mesenteric Artery)^{1,4}

- History: intestinal angina may be present, abdominal pain out of proportion to examination, weight loss, aversion to food (sitophobia), early satiety
- Physical examination
 - Evidence of peripheral vascular disease may be found: bruits, decreased peripheral pulses
 - Abdomen may be initially soft; bowel sounds may be normal, increased, or decreased
 - Rapid progression (hours) to acute abdomen and shock

Mesenteric Venous Thrombosis⁶

- History
 - Periumbilical, colicky abdominal pain >48 hours (75% >7-14 days), nausea, anorexia, vomiting, diarrhea, hematemesis, hematochezia, melena (15%), fecal occult blood (50%)

- Personal or family history of venous thrombosis (50%)

***Nonocclusive Mesenteric Ischemia*⁸**

- History: intensive care unit patients receiving pressors; most are in either septic or cardiogenic shock and have a history of digitalis use

Diagnostic Studies and Laboratory Values

***Blood Tests*^{3,11}**

- Complete blood count: leukocytosis with left shift on smear
- Serum chemistries: elevated serum lactate, metabolic acidosis, elevated serum amylase are common but not specific or sensitive

Radiology

- Abdominal plain film (helps to rule out perforated viscus, small or large bowel obstruction, nephrolithiasis): thumb printing, pneumatosis intestinalis, portal venous air, free peritoneal air^{5,8}
- Abdominal computed tomography (CT): sensitivity (64%) and specificity (92%)¹⁰
 - Oral and intravenous (IV) contrast are the most useful radiological studies to establish the diagnosis of mesenteric venous thrombosis in which mesenteric venous clot and bowel wall edema are seen
- Angiography^{3,5,6,11}
 - Gold standard diagnostic tool for those patients in whom diagnosis remains unclear and hemodynamically stable
 - Useful in the documentation of emboli and anatomy in planning for reconstruction
 - Differentiate occlusive mesenteric ischemia from vasospastic ischemia (seen as a “string of sausages”)

- Ultrasound^{3,5,6,11}
 - 92%-100% specific for proximal stenosis in MVT but only 70%-89% sensitive
 - Not helpful in the presence of abdominal distention or large amounts of bowel gas
 - Usually only useful in ruling out other causes of abdominal pain such as cholelithiasis and cholecystitis
- Magnetic resonance angiography (MRA)^{5,8}
 - Should be considered in the setting of intestinal angina, particularly in patients with renal failure
 - Generally not recommended as MRA takes time to obtain and read, may delay diagnosis, and does not offer therapeutic options unlike angiography

Guide to Acute Management

- A high degree of suspicion for this diagnosis should be maintained in the appropriate clinical setting
- Any suspicion of mesenteric ischemia or intestinal angina should warrant immediate surgical evaluation
- Peritoneal signs warrant immediate surgical evaluation¹
- Patient should be given nothing by mouth with nasogastric suction and IV fluid resuscitation^{1,3,5,6,8,11}
- If pressors are necessary, dopamine is preferred^{1,3,5,8}
- IV antibiotics after blood cultures are drawn; empiric therapy should include imipenem, meropenem, or cefepime and metronidazole
- Penicillin-allergic patients: metronidazole with either levofloxacin or aztreonam
- Imaging studies should be ordered in the following order: abdominal plain film, CT of abdomen with contrast, abdominal angiography^{1,8}

Intestinal Angina

- Exclude other diagnoses with the appropriate laboratory and imaging workup and surgical evaluation

- CT of abdomen with oral and IV contrast or magnetic resonance imaging (MRI) in patients with renal insufficiency

MAE and MAT^{1,5,8}

- Angiography is the gold standard
- Anticoagulation with unfractionated IV heparin is controversial and should not be used; significant gastrointestinal (GI) bleeding can occur if there is infarction
- Papaverine infusion through an angiogram catheter is used to reduce vasospasm
- Thrombolytic therapy is controversial; there are limited data using streptokinase, urokinase, or tissue plasminogen activator; this line of therapy should be reserved for patients diagnosed early (<12 hours) in the disease process and who are poor surgical candidates^{8,9}
- MAE: surgical laparotomy with embolectomy and/or bowel resection is the treatment of choice
- MAT: surgical thrombectomy and bypass with a venous graft or endarterectomy if bypass is not possible or unsuccessful; bowel resection if necessary

Mesenteric Venous Thrombosis^{1,5,8}

- Anticoagulation with unfractionated IV heparin is warranted immediately
- Angiography is the gold standard as it allows definition of the occlusion; if MVT is found, then operative intervention may be avoided if there are no peritoneal signs
- Laparoscopy and resection if bowel infarction is found
- Coumadin (for 6 months to 1 year) if no evidence of infarction is seen on laparoscopy
- Thrombectomy is indicated when the thrombus is recent and is in the superior mesenteric vein
- Patient with polycythemia vera requires phlebotomy⁹

Nonocclusive Mesenteric Ischemia^{4,5,8}

- Primary therapy is treatment of the underlying cause of hypoperfusion
- Angiography by interventional radiology with administration of papaverine is both diagnostic and therapeutic as it will show relaxation of the vasculature, thus making the diagnosis
- Anticoagulation with unfractionated IV heparin is controversial and should not be used
- Significant GI bleeding can occur if there is infarction

**Patient Care Warnings**

- Any suspicion of intestinal angina or mesenteric ischemia warrants immediate surgical evaluation
- Barium studies are contraindicated as they can cause bowel perforation and interfere with other imaging^{5,8}

References

- ③ 1. Sternbach Y, Perler BA: Acute mesenteric ischemia. In Yeo C, ed. Shackleford's Surgery of the Alimentary Tract. Philadelphia, WB Saunders, 2001:17-31.
- ③ 2. Baixauli J, et al. Investigation and management of ischemic colitis. Cleveland Clin J Med 2003;70:920-34.
- ③ 3. Oldenberg W, et al: Acute mesenteric ischemia: A clinical review. Arch Intern Med 2004;24:1054-62
- ③ 4. Vicente David C, et al: Acute mesenteric ischemia. Curr Opin Cardiol 1999:453.
- ③ 5. Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. Gastroenterology 2000;118:954-68.
- ③ 6. Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. New Engl J Med 2001;345:1683-88.
- ③ 7. Schoots IG, Koffeman GI, Legemate DA, et al. Systematic review of survival after acute mesenteric ischaemia according to disease aetiology. Br J Surg 2004;17-27.

- ③ 8. Sreenarasimhaiah J. Diagnosis and management of ischaemic disorders. *Br Med J* 2003;21:1372-76.
- ② 9. Endean ED, Barnes SL, Kwolek CJ, et al. Surgical management of thrombotic acute intestinal ischemia. *Ann Surg* 2001;233:801-08.
- ① 10. Kirkpatrick ID, Kroeker MA, Greenberg HM. Biphasic CT with mesenteric CT angiography in the evaluation of acute mesenteric ischemia: Initial experience. *Radiology* 2003;229:91-98.
- ③ 11. Kurland B, Brandt LJ, Delany HM. Diagnostic tests for intestinal ischemia. *Surg Clin North Am* 1992;72:85-105.

PANCREATITIS

Definition, Etiology, and Epidemiology

- Acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems

ETIOLOGIES

Gallstones

Alcohol

Hypertriglyceridemia

Hypercalcemia

Anatomic obstruction

- Pancreatic mass
- Pancreas divisum
- Ampullary mass
- Duodenal lesions
- Sphincter of Oddi dysfunction

Medications

- Lasix, thiazides, sulfonamides, protease inhibitors, didanosine, estrogen, tamoxifen, salicylates, azathioprine, 6-MP, diprivan, metronidazole, pentamidine, nitrofurantoin, tetracycline, valproic acid

Infections

- Viral (echo, mumps, rubella, coxsackievirus B, Epstein-Barr virus, cytomegalovirus, HIV, hepatitis)
- Bacterial (mycobacteria, leptospirosis, brucellosis)
- Fungal (*Candida*, aspergillosis)
- Parasitic (*Ascaris*, *Ceroplastes sinensis*)

Trauma/endoscopic retrograde cholangiopancreatography (ERCP)

Vascular disease/systemic lupus erythematosus

Posterior perforated peptic ulcer

Idiopathic

Pearls of the History and Physical Examination

History

- Abdominal pain (midepigastric, radiating to back, relieved by sitting forward), nausea and vomiting
- Fever, altered mental status, respiratory distress

Physical Examination

- Abdominal tenderness, decreased bowel sounds, guarding, rigidity, hemodynamic instability
- Cullen's sign (periumbilical ecchymosis in hemorrhagic pancreatitis)
- Grey-Turner's sign (flank ecchymosis in hemorrhagic pancreatitis)
- Fox's sign (inguinal ecchymosis in hemorrhagic pancreatitis)
- Ascites: indicative of severe pancreatitis

Diagnostic Studies and Laboratory Values

Blood Tests

- Lipase (sensitivity 85%-100%; specificity 99% when > three times upper limit of normal in setting of abdominal pain¹) (no clinical utility measuring amylase in addition to lipase)
 - Can expect two times upper limit of normal in renal failure²
- Liver function tests: alanine aminotransferase >150 (96% specific and 48% sensitive for gallstone pancreatitis)³
- Lipid panel: hypertriglyceridemia as potential etiology
- Serum calcium: part of Ranson's criteria
- C-reactive protein (CRP): >150 mg/L 48 hours after admission is very suggestive of severe acute pancreatitis⁴
- Hemoconcentration: marker of severe pancreatitis

Radiographic Studies

- Abdominal plain film: small bowel ileus-sentinel loop; colonic spasm and dilation: colon cutoff sign; calcified gallstones suggesting biliary pancreatitis; evidence of chronic pancreatitis: calcified gland/pancreatic stones, excluding other causes of abdominal pain
- Chest plain film: atelectasis, pleural effusions (marker of severe pancreatitis), elevated diaphragms, infiltrates/acute respiratory distress syndrome (ARDS)
- Sonogram: should be performed in every patient on presentation to evaluate for biliary etiology
- Computed tomography (CT) scan: indicated at presentation if other etiologies of abdominal pain cannot be ruled out
 - May need to be repeated later because necrosis usually takes 24-48 hours to become radiographically apparent
 - Indicated in all cases of *severe pancreatitis* (defined at 24-36 hours in order to evaluate for necrosis/complications)
 - Evaluate for complications in patient with mild disease who does not follow a straightforward clinical course

Guide to Acute Management

Complications	
• Necrosis with or without gland infection	• Bowel obstruction (from ileus, abscess, pseudocyst, or inflammation)
• Retroperitoneal hemorrhage	• Pancreatic ascites
• Acute peripancreatic fluid collection	• Respiratory abnormalities (hypoxemia, atelectasis, effusions, ARDS)

(Continued on following page)

Complications

- Pseudocyst, abscess
- Hypovolemic shock, sepsis, coagulopathy, acute renal failure (usually ischemic acute tubular necrosis)
- Upper gastrointestinal (GI) bleeding due to autodigestion of pancreatic vessels (hemorrhage succus pancreaticus)
- Hypocalcemia
- Splenic vein thrombosis with subsequent gastric variceal bleed
- Subcutaneous fat necrosis

Risk Stratification

- Differentiating mild from severe pancreatitis is critically important in dictating management decisions; severe pancreatitis is pancreatitis associated with any of the following^{4,5}:

- Systemic complications
 - SBP <90 mm Hg
 - PaO₂ ≤60 mm Hg
 - Acute renal failure: creatinine ≥2 mg/dL
 - GI bleeding >500 cc/24 hr
- Unfavorable early clinical prediction scores:
 - Apache II score ≥8
 - Modified Glasgow score ≥3
 - Ranson's (alcohol) or modified Ranson's (gallstone) score ≥3
 - CRP of ≥150 at 48 hours from admission

General

- Nothing by mouth, intravenous fluids (6-10 L/d may be required to maintain intravascular volume)
- Analgesia: there is no evidence to suggest that morphine is contraindicated in acute pancreatitis; may be of benefit over Demerol due to less risk of seizure⁶
- Antiemetic agents

- Nasogastric suction only in patients with refractory nausea/vomiting and gastric/intestinal ileus

Reversal of Underlying Etiology

- Withdrawal of alcohol or precipitating medication(s)
- ERCP indicated within 24-72 hours of admission in patients with pancreatitis and either obstructive jaundice or ascending cholangitis^{7,8}
- Interval cholecystectomy (with preoperative ERCP, magnetic resonance cholangiopancreatography, endoscopic ultrasonography, or intraoperative cholangiogram) is indicated in all cases of biliary pancreatitis after resolution of pancreatic inflammation as there is a >25% chance of recurrent pancreatitis, cholecystitis, or cholangitis within 6 weeks⁹
- Insulin drip and possible exchange transfusion in patients with hypertriglyceridemia
- Fluids and lasix and other measures to reduce serum calcium

Management of Severe Pancreatitis

- Aggressive management of systemic complications, intensive care unit admission
- Dynamic contrast-enhanced CT scan
- Nasojejunal feeding in absence of obstruction (otherwise consider total parenteral nutrition¹⁰)
- If CT scan reveals necrosis, add systemic antibiotics (preferably Primaxin), and continue for 7 days; if there is no improvement or deterioration, perform CT-guided pancreatic tissue aspiration to evaluate for infected necrosis¹¹; if necrosis is sterile, then continue medical management with late surgical débridement reserved for refractory cases
- If necrosis is infected and patient is unstable, early surgical débridement is recommended; if patient is stable, then percutaneous versus endoscopic drainage and débridement

Management of Pseudocyst

- If >5 cm, persisting more than 6 weeks, with clinical symptoms, endoscopic or percutaneous decompression is indicated; otherwise, conservative management indicated
- Consider surgical management: internal anastomoses versus resection if pseudocyst is located in the tail of the pancreas

Management of Pancreatic Abscess

- Percutaneous and surgical drainage have been found to be effective

Indications for Initiating Oral Feeding

- Decreasing pain/nausea medications
- Adequate bowel function (no evidence of obstruction)
- Improving examinations
- Hunger
- Elevated pancreatic enzymes and radiographic abnormalities are not contraindications; start with clear liquids and progress slowly, all carbohydrate-rich meals



Patient Care Warnings

- Always respect acute pancreatitis
- Aggressive volume resuscitation and respiratory support are life-saving
- Conservative management indicated for mild disease
- Severe disease requires CT scan to evaluate for necrosis

References

- ② 1. Gumaste V, Roditis N, Mehta D, et al. Serum lipase levels in nonpancreatic abdominal pain versus acute pancreatitis. *Am J Gastroenterol* 1988;88:2051.
- ② 2. Seno T, Harada H, Ochi K. Serum levels of six pancreatic enzymes as related to the degree of renal dysfunction. *Am J Gastroenterol* 1995;90:2002.
- ① 3. Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: A meta-analysis. *Am J Gastroenterol* 1994;89:1863.
- ② 4. Wilson C, Heads A, Shenkin A, et al. C-reactive protein, antiproteases and complement factors as objective markers of severity in acute pancreatitis. *Br J Surg* 1989;76:177-81.
- ③ 5. Steinberg W, Tenner S. Acute pancreatitis. *New Engl J Med* 1984;330:1198.
- ③ 6. Thompson D. Narcotic analgesic effects on the sphincter of Oddi: A review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* 2001;96:1266-72.
- ① 7. Fan S, Lai E, Mok P, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *New Engl J Med* 1993;328:228.
- ① 8. Folsch UR, Nitsche R, Ludtke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. *New Engl J Med* 1997;336:237.
- ② 9. Elfstrom J. The timing of cholecystectomy in patients with gallstone pancreatitis. A retrospective analysis of 89 patients. *Acta Chir Scand* 1978;144:487.
- ① 10. Abou-Assi S, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: Results of a randomized comparative study. *Am J Gastroenterol* 2002;97:2255.
- ② 11. Gerzof SG, Banks PA, Robbins AH, et al. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. *Gastroenterology* 1987;93:1315.

TYPHLITIS

Definitions, Etiology, and Epidemiology

- First reported in children^{1,2} and occurs in immunosuppressed patients as a life-threatening necrotizing enterocolitis
- Although studied extensively in children,³ it has been described in adults in the context of treated and untreated acute myeloid leukemia⁴ but also seen in immunosuppression,⁵ solid tumors, multiple

myeloma, aplastic anemia, AIDS, cyclic neutropenia,⁶ and autologous bone marrow transplantation⁷

- Also consider patients who are taking drugs that may precipitate neutropenia; for example, methimazole⁸
- Pathophysiology is not well understood and may be a combination of cytotoxic drugs, immunosuppression or profound neutropenia, and host barrier compromise with mucosal injury

Pearls of the History and Physical Examination

History

- Recent chemotherapy, stomatitis, fever, abdominal pain (right lower quadrant pain), abdominal distention, nausea, vomiting, bloody diarrhea,^{4,9} clinical findings similar to those of appendicitis

Physical Examination

- Signs of peritonitis and hypotension suggest perforation
- Decreased bowel sounds

Diagnostic Studies and Laboratory Values

Blood Tests

- Complete blood count: absolute neutrophil count: white blood cells $\times$ (% neutrophils + % bands)
- Blood cultures (two sets from different sites), stool cultures
- Lactic acid (high levels may indicate bowel wall compromise)

Radiographic Studies

- Kidney, ureter, bladder: pneumatosis is a poor prognostic indicator
- Ultrasound
 - Symptomatic patients with bowel wall thickening

have a poor prognosis compared with patients without this finding^{10,11}

- Mural thickness of more than 10 mm is associated with poorer outcome among patients with typhlitis¹¹
- Computed abdomen tomography
 - Can help differentiate typhlitis from appendicitis, related abscess, and pseudomembranous colitis¹²
 - Findings include bowel wall thickening, pneumatosis, right-sided colonic inflammation,^{13,14} fascial thickening, and mesenteric lymphadenopathy

Guide to Acute Management

- Surgical consultation should be obtained early
- Conservative medical management includes bowel rest, nasogastric tube decompression, intravenous (IV) fluids, and broad spectrum antibiotics as initial steps
 - See section titled Neutropenic Fever for antibiotic guide as polymicrobial infections are observed
 - Note: include Flagyl 500 mg IV 3 times/day, especially if surgery is being considered¹⁵
 - See section titled Sepsis for patient management if criteria are met
 - Total parenteral nutrition has been used in some instances^{4,16,17}
 - Granulocyte-colony stimulating factor (filgastrim; 5 µg/kg subcutaneously) can be used for neutropenic recovery^{5,18}
 - Granulocyte transfusion can be done but may take 48 hours to coordinate with the blood bank
- Surgical management is appropriate for those with pneumatosis, perforation, peritonitis, lower gastrointestinal bleeding with resection of necrotic bowel minimally or right hemicolectomy—neutropenia should not be a deterrent^{4,5,6,19-21}; surgery may carry lower mortality risk than medical management alone^{18,19,22}



Patient Care Warnings

- Barium enema is potentially dangerous due to risk of perforation in setting of necrotic bowel
- Beware of fungemia if clinical picture does not improve in 48-72 hours

References

- ③ 1. McNamara MJ, Chalmers AG, Morgan M, et al. Typhlitis in acute childhood leukaemia: Radiological features. *Clin Radiol* 1986;37:83-86.
- ③ 2. Wu SF, Peng CT, Tsai FJ, et al. Typhlitis in acute childhood leukemia. *Chung Hua Min Kuo Hsiao Erh Ko I Hsueh Hui Tsa Chih* 1996;37:208-10.
- ② 3. Kliegman RM, Hack M, Jones P, et al. Epidemiologic study of necrotizing enterocolitis among low-birth-weight infants: Absence of identifiable risk factors. *J Pediatr* 1982;100:440-44.
- ② 4. Hsu TF, Huang HH, Yen DH, et al. ED presentation of neutropenic enterocolitis in adult patients with acute leukemia. *Am J Emerg Med* 2004;22:276-79.
- ② 5. Choi JH, Lee JM, Shin WS, et al. Necrotizing enterocolitis: Experience of 27 cases from a single Korean institution. *Int J Hematol* 2000;72:358-61.
- ③ 6. Bavaro MF. Neutropenic enterocolitis. *Curr Gastroenterol Rep* 2002;4:297-301.
- ③ 7. Or R, Mehta J, Nagler A, et al. Neutropenic enterocolitis associated with autologous bone marrow transplantation. *Bone Marrow Transplant* 1992;9:383-85.
- ③ 8. Chen DF, Chao IM, Huang SH. Neutropenic colitis with cecal perforation during antithyroid therapy. *J Formos Med Assoc* 2003;102:644-46.
- ③ 9. Moir CR, Scudamore CH, Benny WB. Typhlitis: Selective surgical management. *Am J Surg* 1986;151:563-66.
- ② 10. Gorschluter M, Marklein G, Hofling K, et al. Abdominal infections in patients with acute leukaemia: A prospective study applying ultrasonography and microbiology. *Br J Haematol* 2002;117:351-58.
- ② 11. Cartoni C, Dragoni F, Micozzi A, et al. Neutropenic enterocolitis in patients with acute leukemia: Prognostic significance of bowel wall thickening detected by ultrasonography. *J Clin Oncol* 2001;19:756-61.

- ③ 12. de Brito D, Barton E, Spears KL, et al. Acute right lower quadrant pain in a patient with leukemia. *Ann Emerg Med* 1998;32:98.
- ② 13. Kirkpatrick ID, Greenberg HM. Gastrointestinal complications in the neutropenic patient: Characterization and differentiation with abdominal CT. *Radiology* 2003;226:668-74.
- ② 14. Sloas MM, Flynn PM, Kaste SC, et al. Typhlitis in children with cancer: A 30-year experience. *Clin Infect Dis* 1993;17:484-90.
- ② 15. Vermeylen D, de Laet MH, Pardou A, et al. Neonatal necrotizing enterocolitis: From reduction of mortality to reduction of morbidity. *Acta Anaesthesiol Belg* 1985;36:153-59.
- ③ 16. Heird WC, Gomez MR. Total parenteral nutrition in necrotizing enterocolitis. *Clin Perinatol* 1994;21:389-409.
- ② 17. Moss RL, Das JB, Raffensperger JG. Necrotizing enterocolitis and total parenteral nutrition-associated cholestasis. *Nutrition* 1996;12:340-43.
- ③ 18. Colovic N, Rajic Z, Sretenovic M, et al. Neutropenic enterocolitis in acute myeloid leukemia. *Acta Chir Iugosl* 2004;51:127-31.
- ② 19. Chirletti P, Barillari P, Sammartino P, et al. The surgical choice in neutropenic patients with hematological disorders and acute abdominal complications. *Leuk Lymphoma* 1993;9:237-41.
- ② 20. Villar HV, Warneke JA, Peck MD, et al. Role of surgical treatment in the management of complications of the gastrointestinal tract in patients with leukemia. *Surg Gynecol Obstet* 1987;165:217-22.
- ③ 21. Urbach DR, Rotstein OD. Typhlitis. *Can J Surg* 1999;42:415-19.
- ③ 22. Mower WJ, Hawkins JA, Nelson EW. Neutropenic enterocolitis in adults with acute leukemia. *Arch Surg* 1986;121:571-74.

INFLAMMATORY BOWEL DISEASE

Ulcerative Colitis (UC)

Definitions, Etiology, and Epidemiology

- Recurring episodes of inflammation limited to the mucosal layer of the colon

- Currently affects 250,000-500,000 people in the United States; incidence is 2-7/100,000 population per year
- Onset in second to third decades of life; all ethnic groups affected although whites more so than non-whites

Pearls of the History and Physical Examination

History

- Initial presentation
 - Classic history of a gradual onset of symptoms preceded by rectal bleeding
 - 33% distal colitis, 33% left-sided colitis, 33% pancolitis (<10% with fulminant disease)
- Classic symptoms
 - Diarrhea with or without blood, tenesmus, urgency, rectal pain, passage of mucus without diarrhea, weight loss, malaise, crampy abdominal pain

Physical Examination

- Abdominal tenderness (generalized), bright red blood per rectum, pallor, pyoderma gangrenosum

Extraintestinal Manifestations

- Peripheral arthritis (large joints), ankylosing spondylitis, pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis, uveitis, episcleritis, hypercoagulability, and autoimmune hemolytic anemia

Diagnostic Studies and Laboratory Values

Endoscopy with Biopsies (Definitive)

- Endoscopic findings: loss of typical vascular pattern; increased granularity, friability, and ulceration; pres-

ence of petechiae and exudates; symmetric, circumferential, continuous involvement of colon wall

- Histological findings: separation, distortion, and atrophy of crypts; loss of mucin in goblet cells, acute/chronic inflammatory cells in lamina propria; crypt abscesses

Radiology

- Computed tomography scan: usually with nonspecific findings such as thickened bowel wall
- Small bowel follow through (SBFT): helps rule out Crohn’s disease

Blood Tests

- Serological tests: antineutrophil cytoplasmic antibodies (pANCA); anti-*Saccharomyces cerevisiae* antibodies (ASCA): unreliable but positive in large numbers of UC and Crohn’s disease patients.

Guide to Acute Management

- Therapeutic decisions based on anatomic extent and clinical severity (not histological extent): therefore, full colonoscopy essential after diagnosis is made

DEFINITION OF SEVERITY ^{1,2}			
Mild	Moderate	Severe	Fulminant
<4 stools per day with or without blood No systemic signs of toxicity	4 stools per day Minimal signs of toxicity (low-grade fever, anemia not requiring transfusion, minor abdominal pain)	6 bloody stools per day Evidence of toxicity (tachycardia, anemia, fever, elevated ESR)	>10 bowel movements per day Continuous bleeding with blood transfusion requirement

(Continued on following page)

DEFINITION OF SEVERITY^{1,2} (Continued)

Mild	Moderate	Severe	Fulminant
Normal erythrocyte sedimentation rate (ESR)		Poor nutritional state	Toxicity Abdominal tenderness and distention Colonic dilation on abdominal plain films

Mild-to-Moderate Distal Colitis

- Proctitis and proctosigmoiditis³
- First-line agents are topical 5-ASA compounds
 - Superior to topical steroids or oral aminosalicylates⁴
 - Use mesalamine suppositories for proctitis⁵; start with mesalamine enema 4 g pr QHS for proctosigmoiditis and increase to twice daily if needed⁶
- Topical steroids (hydrocortisone 100 mg pr twice daily) may be given twice daily for symptomatic benefit⁴
 - No evidence that maintenance therapy will prevent relapse
- For patients who do not respond to or do not tolerate topical therapy, some studies suggest that the combination of oral/topical aminosalicylates may be more effective than either alone⁷
 - Sulfasalazine (4-6 g/d in 4 divided doses), mesalamine (2-4.8 g/d in 3 divided doses), balsalazide (6.75 g/d in 3 divided doses), olsalazine (1.5-3 g/d in 3 divided doses)
- Oral steroids may be necessary for patients refractory to above treatments
- In active disease, patient requires 4-6 weeks of therapy for complete healing prior to initiation of maintenance regimen
- Maintenance of remission
 - Mesalamine suppositories (500 mg bid) for proctitis

- Mesalamine enemas (2-4 g every day, every other day, or every third day)⁸
- Oral aminosalicylates (sulfasalazine 2 g/d, olsalazine 1 g/d, Eudragit-S-coated mesalamine 3.2 g/d, and balsalazide 3-6 g/d)
- Oral and topical more effective than either alone⁹

Mild-to-Moderate Extensive Colitis

- Pancolitis or any disease extending proximal to sigmoid
- Sulfasalazine (4-6 g/d) first line
 - If not tolerated, use other aminosalicylates such as balsalazide, olsalazine, and Eudragit-S-coated mesalamine (dose: 2-4.8 g/d of active 5-ASA moiety)
 - May combine with topical therapy for symptomatic benefit
- Prednisone 40-60 mg/d reserved for those patients refractory to above therapy
 - No evidence for specific taper, although usually 40-60 mg/d until clinical improvement, then 5-10 mg/week taper until 20 mg/d, then 2.5 mg/week
- Azathioprine/6-MP 1.5-2.5 mg/kg/d for patients who cannot be weaned off steroids¹⁰; limited by slow onset of action (3-6 months)
- Maintenance of remission
 - Sulfasalazine (2-4 g/d), may achieve higher 5-ASA doses with newer aminosalicylates
 - Most studies recommend permanent maintenance with first UC flare
 - Azathioprine/6-MP well tolerated and effective in maintaining remission as steroid-sparing agents or for patients who are steroid dependent

Severe Colitis

- Severe symptoms despite oral steroids, oral aminosalicylates, and topical medications
- Intravenous (IV) steroids (hydrocortisone 100 mg IV

every 8 hours, methylprednisolone 30 mg IV every 12 hours)

- IV fluids, bowel rest, serial physical examination, serial abdominal x-rays
- No proven therapeutic benefit from antibiotics (unless fulminant) but usually included in treatment protocols (IV Flagyl, IV ciprofloxacin)
- No proven therapeutic benefit from total parenteral nutrition
- No proven benefit from addition of oral/topical aminosalicylates to steroid therapy, although usually included
- Consult for surgery; 40% fail medical management¹¹
- For those who fail medical therapy after 7 days, should be offered therapy with cyclosporine (2-4 mg/kg/d) or referred for surgery; patients with steroid-refractory UC, cyclosporine is beneficial in preventing surgery in the acute stage¹²

Fulminant Colitis (Toxic Megacolon)

- Toxic megacolon is a severe attack of colitis with total or segmental dilation of the colon (diameter >6 cm); considered toxic if the colon wall is persistently surrounded by air on kidney, ureter, bladder (KUB) test in the presence of two or more of the following characteristics:
- Tachycardia (>100 beats per minute), temperature >101.5°F, leukocytosis >10,000 cells/mm³, hypoalbuminemia <3.0 g/dL
- Management: as above, except look for clinical improvement within 72 hours; if not, consider surgery¹³
 - Small bowel decompression; broad spectrum antibiotics; avoid opioids and anticholinergics; rotate patient frequently into prone knee-elbow position to relieve gas

INDICATIONS FOR SURGERY

Absolute Indications	Other Indications
Exsanguinating hemorrhage (3%)	Severe colitis with or without toxic megacolon unresponsive to medical therapy
Perforation (2%-3%)	Less severe colitis with medically intractable symptoms
Documented/strongly suspected carcinoma	Severe, progressive pyoderma gangrenosum (which parallels colitis) Hemolytic anemia refractory to steroids/splenectomy



Patient Care Warnings

- Cancer surveillance: for all patients who are surgical candidates, annual/biannual colonoscopies with biopsies at 10-cm intervals recommended (avoiding periods of clinical relapse) after 8-10 years of colitis

Crohn's Disease (CD)

Definitions, Etiology, and Epidemiology

- A nonspecific inflammation of any segment of the intestine with discontinuous or skip areas of ulceration and granulomatous, fissuring, or transmural inflammation
- Incidence is 5/100,000; prevalence 50/100,000; most common in the second and third decade of life

Pearls of the History and Physical Examination

History

- Initial presentation: insidious onset (occasionally fulminant with or without toxic megacolon)
 - Variable location: ileocecal (50%), ileal (25%), colon (20%), upper gastrointestinal (GI) or perirectum (5%)
- Classic symptoms: chronic/nocturnal diarrhea with or without blood, abdominal pain, fatigue, bowel obstruction, weight loss, fever, chills, night sweats, aphthous ulcers, odynophagia/dysphagia, gastric outlet obstruction, evidence of fat malabsorption, fistula formation, abscess formation

Physical Examination

- Abdominal tenderness (generalized), bright red blood per rectum, pallor, fistulae, abscesses
- Extraintestinal manifestations: peripheral arthritis (large joints), ankylosing spondylitis/sacroiliitis, pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis, uveitis, hypercoagulability, nephrolithiasis (oxalate type), cholelithiasis, and autoimmune hemolytic anemia

Diagnostic Studies and Laboratory Values¹⁴

Endoscopy

- Upper/lower GI endoscopy to confirm diagnosis, assess location, or obtain tissue
 - Endoscopic findings: focal ulcerations adjacent to areas of normal-appearing mucosa along with polypoid mucosal changes creating a cobblestone appearance; skip areas present
 - Histological findings: focal ulcerations, acute and chronic inflammation, granulomas (30%)

- Wireless capsule endoscopy to identify small bowel disease (drawbacks include inability to take biopsies)

Radiology

- Contrast radiography (air contrast barium enema, SBFT, enteroclysis) to confirm disease location (especially in areas not accessible via endoscopy), intestinal complications
 - “String sign”: segmental duodenal stricturing, antral narrowing, thickened bowel wall, separation of bowel loops
- Abdominal ultrasound, computed tomography, magnetic resonance imaging to delineate intra-abdominal masses

Guide to Acute Management

DEFINITION OF SEVERITY ¹⁴			
Mild-to-Moderate Disease	Moderate-to-Severe Disease	Severe-to-Fulminant Disease	Remission
Ambulatory patients who tolerate oral alimentation without dehydration No toxicity (fevers, rigors, prostration) Abdominal tenderness, painful mass, obstruction >10% weight loss	Patients who have failed to respond to therapy for mild-moderate disease OR Those with more prominent symptoms of fever, significant weight loss, abdominal pain/tenderness, nausea, vomiting, or significant anemia	Patients with persistent symptoms despite introduction of steroids OR Patients presenting with high fever, persistent vomiting, evidence of obstruction, rebound tenderness, cachexia OR Evidence of an abscess	Patients who are asymptomatic or without inflammatory sequelae, i.e., patients who have responded to acute medical or surgical intervention

Mild-to-Moderate Disease

- Ileal disease
 - Mesalamine 2-4.8 g daily in divided doses¹⁵
 - Antibiotics: to be used in patients who do not tolerate or respond to 5-ASA compounds
 - Ciprofloxacin 500 mg PO twice daily for 6 weeks, then 500 mg PO daily for 6 weeks
- Ileocolonic or colonic disease
 - Sulfasalazine 1-6 g/d in divided doses,^{16,17} mesalamine 2-4.8 g/d in divided doses,^{18,19} metronidazole 10-20 mg/kg more effective for ileocolitis than isolated ileal disease (no long-term data)²⁰; limited data for ciprofloxacin 1 g/d
- Esophageal or gastroduodenal or jejunoileal
 - Overall lack of evidence
 - Reported in uncontrolled studies to respond to proton pump inhibitors
- Response usually occurs within several weeks after which point, responders should be considered for maintenance therapy and nonresponders should be treated as moderate-to-severe disease

Moderate-to-Severe Disease

- Prednisone 40 mg orally every day with taper once clinical response achieved (5-10 mg weekly until 20 mg, then 2.5 mg weekly)
- 50% of patients will become steroid-dependent or steroid-resistant and will require adjunctive agents such as azathioprine 2.5 mg/kg²¹ or methotrexate 25 mg SC or IM every week^{22,23}
- For those who do not respond to aminosalicylates, prednisone, or immunomodulators, consider infliximab 5 mg/kg^{24,25} (standard of care); no significant long-term benefit from elemental, liquid polymeric diets

Severe-to-Fulminant Disease

- IV fluids, electrolyte repletion, and transfusions in the setting of anemia
- Surgical consultation for obstruction, tender abdominal mass
 - Abdominal mass should be further evaluated to rule out abscess, which would require surgical/percutaneous drainage
- Empiric antibiotics in the setting of an inflammatory mass
- Bowel rest, total parenteral nutrition for those patients who are severely ill or show evidence of obstruction
- IV steroids once abscess has been ruled out (prednisone 40-60 mg in divided doses)
- Infliximab usually given before cyclosporine or tacrolimus
- Consider IV cyclosporine or tacrolimus if no response to steroids^{26,27}
- Failure to respond to steroids or cyclosporine/tacrolimus should lead to surgical intervention

Perianal Disease

- Suppurative disease requires surgical drainage
- Variety of options for nonsuppurative disease: metronidazole with or without ciprofloxacin,^{28,29} azathioprine, cyclosporine, tacrolimus, infliximab for refractory fistulae³⁰

Maintenance Therapy

- Initially try mesalamine 3 g/d³¹
- Trials with 5-ASA compounds have proven ineffective in maintenance of steroid-induced remission.
- Other alternatives: controlled release budesonide 6 mg/d, azathioprine (2.5 mg/kg) and 6-MP (1.5 mg/kg), infliximab 5 mg/kg every 8 weeks; long-term effects and efficacy of these drugs remain uncertain

References

- ③ 1. Hanauer S. Inflammatory bowel disease. *N Engl J Med* 1996;334:841-48
- ② 2. Truelove SC, Witts LJ. Cortisone in ulcerative colitis: Final report on a therapeutic trial. *Br Med J* 1955;2:1041-45.
- ③ 3. Kornbluth A, Sachar D. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology practice parameters committee. *Am J Gastroenterol* 2004;1371-85.
- ① 4. Cohen RD, Woseth DM, Thisted RA, et al. A meta-analysis overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000;95:1263-76.
- ① 5. Campieri M, de Franchis R, Bianchi Porro G, et al. Mesalazine suppositories in the treatment of ulcerative proctitis or distal proctosigmoiditis: A randomized controlled trial. *Scand J Gastroenterol* 1990;25:663.
- ① 6. Campieri M, Lanfranchi GA, Bazzochi G, et al. Treatment of ulcerative colitis with high dose 5-aminosalicylic acid enemas. *Lancet* 1981;2:270.
- ① 7. Safdi M, DeMicco M, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997;92:1867-71.
- ③ 8. Miner P, Daly R, Nester T, et al. The effect of varying dose intervals of mesalamine enemas for the prevention of relapse in distal ulcerative colitis. *Gastroenterology* 1994;106:A723.
- ② 9. D'Albasio G, Pacini F, Camarri E, et al. Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: A randomized double-blind study. *Am J Gastroenterol* 1992;1997:1143-47.
- ② 10. Rosenberg JL, Wall AJ, Settles RH, et al. A controlled trial of azathioprine in the treatment of chronic ulcerative colitis. *Gastroenterology* 1973;64:793-801.
- ③ 11. Kornbluth A, Marion J, Bharuca S, et al. The treatment of severe ulcerative and Crohn's colitis: A critical analysis of the defined trials. *J Clin Gastroenterol* 1995;18:242-46.
- ① 12. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841-45.
- ③ 13. Truelove SC, Mark CG. Toxic megacolon. *Clin Gastroenterol* 1981;10:107-17.
- ③ 14. Hanauer SB, Sandborn W. Management of Crohn's disease in adults. *Am J Gastroenterol* 2001;96:635-43.
- ① 15. Hanauer SB, Stromber U. Oral pentasa in the treatment of active Crohn's disease: A meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004;2:379.
- ① 16. Summers RW, et al. National cooperative Crohn's disease

- study: Results of drug treatment. *Gastroenterology* 1979;77:847-69.
17. Van Hees PAM, et al. Effect of sulphasalazine in patients with active Crohn's disease: A controlled double-blind study. *Gut* 1981;22:404-09.
 18. Tremaine WJ, et al. A randomized, double-blind, placebo-controlled trial of the oral mesalamine preparation Asachol in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994;19:278-82.
 19. Prantera C, et al. Mesalamine in the treatment of mild to moderate active Crohn's ileitis: Results of a randomized, multicenter trial. *Gastroenterology* 1999;116:521-26.
 20. Sutherland L, et al. Double-blind, placebo-controlled trial of metronidazole in Crohn's disease. *Gut* 1991;32:1071-75.
 21. Modigliani R, et al. Mesalamine in Crohn's disease with steroid induced remission: Effect on steroid withdrawal and remission maintenance. *Groupe d'etudes therapeutiques des affections inflammatoires digestives. Gastroenterology* 1996;110:688-93.
 22. Sandborn WJ, et al. Lack of effect of intravenous administration on time to respond to azathioprine for steroid-treated Crohn's disease. *Gastroenterology* 1999;117:527-35.
 23. Feagan BG, et al. Methotrexate for the treatment of Crohn's disease: North American Crohn's Study Group Investigators. *N Engl J Med* 1995;332:292-97.
 24. Sandborn WJ, Hanauer SB. Antitumor necrosis factor therapy for inflammatory bowel disease: A review of agents, pharmacology, clinical results, and safety. *Inflamm Bowel Dis* 1999;5:119-33.
 25. Targan SR, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;337:1029-35.
 26. Egan LJ, Sandborn WJ, Tremaine WJ. Clinical outcome following treatment of refractory inflammatory and fistulizing Crohn's disease with intravenous cyclosporine. *Am J Gastroenterol* 1998;93:442-48.
 27. Fellermann K, et al. Steroid-unresponsive acute attacks of inflammatory bowel disease: Immunomodulation by tacrolimus (FK506). *Am J Gastroenterol* 1998;93:1860-66.
 28. Bernstein LH, et al. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980;79:357-65.
 29. Brandt LJ, et al. Metronidazole therapy for perineal Crohn's disease: A follow-up study. *Gastroenterology* 1982;83:383-87.
 30. Present DH, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-1405.
 31. Messori A, Brignola C, Trallor G, et al. Effectiveness of 5-ASA for maintaining remission in patients with Crohn's disease: A meta-analysis. *Am J Gastroenterol* 1994;89:2116.

HEPATIC ENCEPHALOPATHY

Definition, Epidemiology, and Etiology

- Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that may complicate acute or chronic liver failure¹; it can also be observed in patients with portosystemic shunting
- Present in 50%-70% of all patients with cirrhosis (including those with subclinical abnormalities shown only by psychometric testing)
- The pathophysiology of HE remains poorly defined.
- Accumulation of nitrogenous substances (predominantly ammonia) in brain as a result of poor hepatic function and portosystemic shunting has traditionally been considered the most likely mechanism²
- A precipitating factor can be found in 90% of cases

Increased Ammonia Production	Not Related to Ammonia Production
Uremia/azotemia (30%)	Sedatives/benzodiazepines (25%)
Gastrointestinal (GI) bleeding (20%)	Barbiturates
Dehydration	Hypoxia
Metabolic alkalosis/hypokalemia (15%)	Hypoglycemia
Check for diuretic use	Hypothyroidism
Constipation (5%)	Anemia
Excessive dietary protein (10%)	Portosystemic shunts (transjugular intrahepatic, surgical, or spontaneous)
Infection (5%); always rule out SBP	

Pearls of the History and Physical Examination

History

- Hallmark of HE is an abnormal mental status that can range from subtle inattentiveness (diagnosed by psychometric tests) to a deep coma

- Look for precipitating factors; review patient medication list and recent changes in protein intake

Physical Examination

- Asterixis is not specific and can be seen in other metabolic encephalopathies (uremia, respiratory failure, and congestive heart failure)
- Look for underlying cause of liver disease, signs of chronic liver disease (jaundice, spider angiomas, ascites, palmar erythema, gynecomastia)

STAGING OF HE ³			
Grade	Level of Consciousness	Personality and Behavior	Neurological Signs
0	Normal	Normal	None
Subclinical	Normal	Normal	Abnormal psychometric tests
1	Inverted sleep pattern, restlessness	Forgetfulness, mild confusion, agitation, irritability	Tremor, impaired handwriting, incoordination
2	Lethargy, slow responses	Disorientation in time, amnesia, inappropriate behavior	Asterixis, dysarthria, ataxia, hypoactive reflexes
3	Somnolence, confusion	Disorientation in place, aggressive behavior	Asterixis, hyperactive reflexes, Babinski's sign
4	Coma	None	Decerebration

Diagnostic Studies and Laboratory Values

- Diagnosis of HE is clinical and one of exclusion
- Differential diagnoses include any cause of altered mental status (AMS) (metabolic, infection, intracranial vascular events, intracranial mass)
- Blood tests

- Ammonia levels do not correlate with mental status changes and have little clinical value in establishing the diagnosis of HE or following progress of patients; a normal ammonia level does not rule out HE and should not delay initiation of therapy^{4,5}
- Complete blood count: anemia and leukocytosis
- Serum chemistries: alkalosis, hypokalemia, hypoglycemia, blood urea nitrogen, creatinine (assess renal function), liver function tests to assess presence or degree of liver disease
- Computed brain tomography if neurological examination is asymmetrical (with subsequent lumbar puncture if suspicion for meningitis exists)
- Urine toxicology screen (other causes of AMS)

Guide to Acute Management^{6,7}

Supportive Care

- Most critical step during all stages of HE
- Consider endotracheal intubation in patients with deep coma for airway protection
- Cerebral edema: presents with hypertension, bradycardia, irregular respirations, decerebrate posturing, and epileptiform activity (see section titled Acute Liver Failure)
- Management of agitation includes physical restraints and medication; avoid benzodiazepines; haloperidol is a safe choice; phenytoin and gabapentin are preferred drugs if seizure management needed⁸

Identify and Remove Precipitating Factors

- Always evaluate for GI bleeding, ascites complicated with SBP, hypokalemia, and volume depletion
- The presence of large spontaneous portosystemic shunts should be sought in patients with recurrent episodes of HE despite medical therapy when a

precipitating factor is not found; Doppler ultrasound and angiogram are recommended

Reduction of Nitrogenous Load From Gut

- Nutrition
 - If oral feeding is not feasible, hold oral intake for 24-48 hours
 - Intravenous (IV) glucose (D5NS) should be administered until and if improvement occurs
 - Start tube feeding if patient remains unconscious for more than 48 hours
- Protein intake starts at 0.5 kg/d and should be titrated up to 1.5 kg/d

Bowel Cleansing and Reduction of Ammonia Production

- Nonabsorbable disaccharides: there are insufficient data to support or refute the use of these agents⁹
 - Lactulose: start with 45 cc every hour until evacuation occurs, then titrate dose and frequency to obtain 2-3 soft bowel movements/day (usually 15-45 cc every 8-12 hours); can be given orally or by nasogastric tube; retention enema can be used (300 cc in 1 L of water)
 - Above regimen is aggressive; therefore, frequency may be decreased as needed; beware of hypokalemia, hyponatremia, and volume depletion during catharsis
- Oral antibiotics
 - Recommended when HE is refractory to lactulose
 - Neomycin (1-2 g/d orally), metronidazole (250 mg orally every 8-12 hours), or rifamixin (1200 mg/d) can be used

Drugs That Affect Neurotransmission

- These are not part of standard treatment
- Flumazenil (1 mg bolus IV) indicated only for patients with HE and suspected benzodiazepine intake

Assess for Need of Long-Term Therapy

- At discharge, two factors need to be considered:
 - Control of potential precipitating factors: lactulose to avoid constipation, prophylaxis of esophageal varices bleeding, prophylaxis for SBP, judicious use of diuretics, avoidance of psychoactive and sedative medication
 - Liver transplantation evaluation



Patient Care Warnings

- Identification and correction of precipitating factors are cornerstone of treatment
- Start empiric treatment if HE suspected
- A normal ammonia level does not rule out HE; ammonia levels do not correlate accurately with mental status changes
- Untreated HE can progress into deep coma and cerebral edema

References

- ③ 1. Gitlin N. Hepatic encephalopathy. In Zakim D, Boyer TD, eds. *Hepatology: A Textbook of Liver Disease*, 3rd ed. Philadelphia, WB Saunders, 1996, pp 605-17.
- ③ 2. Blei AT. Infection, inflammation and hepatic encephalopathy, synergism redefined. *J Hepatol* 2004;40:327-30.
- ③ 3. Riordan SM, Williams R. Treatment of hepatic encephalopathy. *New Engl J Med* 1997;337:473-79.
- ② 4. Lockwood AH, et al. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. *J Cereb Blood Flow Metab* 1991;11:337-41.
- ② 5. Kramer L, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. *Hepatology* 2000;31:30-34.
- ③ 6. Blei AT, Cordoba J. Practice guidelines: Hepatic encephalopathy. *Am J Gastroenterol* 2001;96:1968-76.
- ③ 7. Fitz JG. Hepatic encephalopathy, hepatopulmonary syndromes, hepatorenal syndrome, coagulopathy and endocrine complications of liver disease. In Feldman M, Friedman LS,

- Brandt LJ (eds): Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 7th ed. 2002:1543-50.
- ③ 8. Prabhakar S, Bhatia R. Management of agitation and convulsions in hepatic encephalopathy. *Indian J Gastroenterol* 2003;22 (Suppl 2):S50-S53.
 - ① 9. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: Systematic review of randomised trials. *Br Med J* 2004;328:1046.

SPONTANEOUS BACTERIAL PERITONITIS

Definitions, Etiology, and Epidemiology

- Spontaneous bacterial peritonitis (SBP) is spontaneous infection of ascitic fluid in the absence of a surgical or other intra-abdominal source of infection
- Presence of more than 250 polymorphonuclear (PMN) cells per mm³ of ascitic fluid with a positive culture helps establish diagnosis²
- Pathophysiology involves translocation of bacteria from the intestinal lumen to surrounding lymph nodes, with subsequent bacteremia and infection of ascitic fluid³
- Primary pathogens are aerobic gram-negative bacteria (*Escherichia coli* and *Klebsiella*)
- Frequency of episodes caused by gram-positive bacteria (*Staphylococcus pneumoniae* and other *Staphylococcus*) is increasing¹

Pearls of the History and Physical Examination

History

- Etiology of ascites (ascites due to portal hypertension represents highest-risk patient population)
- Clinical manifestations in order of decreasing frequency include fever, abdominal pain, mental status change, abdominal tenderness, diarrhea, ileus, hypotension, and hypothermia⁴
- Patients are often asymptomatic

Physical Examination

- Stigmata of cirrhosis (spider angiomas, palmar erythema, caput madusae, etc.)
- SBP in noncirrhotic ascites is extremely rare
- Rigid surgical abdomen rarely develops because visceral and parietal peritoneal layers are separated by ascites⁵

Diagnostic Studies and Laboratory Values

Ascitic Fluid Analysis (From Diagnostic Paracentesis)

- PMN count $>250/\text{mm}^3$ with positive culture is highly suggestive of SBP¹
- In hemorrhagic ascites or traumatic paracentesis, the PMN count can be adjusted by subtracting one PMN for every 250 red blood cells in the ascitic fluid
- Send fluid for bacterial culture
 - Bedside inoculation of blood culture bottles increases sensitivity from 50% to 80%⁶
 - Culture volume: 10-20 mL inoculum (93%) has a higher culture positivity rate than a 1-mL inoculum (53%)⁷
 - Other ascitic fluid studies can be used to distinguish SBP from secondary bacterial peritonitis (see below)
 - Due to poor culture yield and incorrect culture technique, many patients are mistakenly given a diagnosis of culture-negative neutrophilic ascites (>250 PMN/ mm^3 with negative culture) when they really have SBP
 - Gram's stain is not helpful
 - Low organism counts may lead to false-negative results
 - Negative culture with presence of Gram's stain may muddy the clinical picture

Blood Tests

- Complete blood count: peripheral leukocytosis does not lead to an elevated ascitic fluid PMN count⁸
- Serum chemistries; baseline liver function tests; blood, urea, nitrogen; creatinine

Guide to Acute Management

- Initiate empiric antibiotics before obtaining culture results with a high index of suspicion or when >250 PMN/mm³
 - A third-generation cephalosporin (cefotaxime 2 g IV q8h or ceftriaxone 2 g IV qd depending on renal function) covers 95% of expected causal bacteria⁹
 - Cephalosporin allergy: fluoroquinolones, beta lactam–beta lactamase inhibitor combination, imipenem-cilastatin, meropenem¹⁰
 - Treat for a minimum of 5 days; just as effective as a 10-day course of therapy¹¹
- Repeat paracentesis should be performed in 48-72 hours if no clinical response seen
 - Decrease of $<25\%$ in PMN count is considered failure of antibiotic treatment; consider switching antibiotics empirically or based on susceptibilities
 - In culture-negative neutrophilic ascites, repeat paracentesis on therapy documenting a decrease in PMN count can be helpful in showing a treatment response
 - Consider secondary bacterial peritonitis if a patient is not appropriately responding to antibiotics or multiple organisms grow from culture
- IV albumin administration leads to less irreversible renal impairment (10% vs. 33%) and lower mortality both during hospitalization (10% vs. 29%) and three months postdischarge (22% vs. 41%)¹²

- Give 1.5 g albumin/kg body weight within 6 hours of SBP diagnosis and 1 g albumin/kg body weight on day three¹²

SBP Prophylaxis in Patients With Ascites

Risk Factors for Recurrent SBP

- Ascitic fluid total protein (AFTP) concentration <1 g/dL
- Serum bilirubin >2.5 mg/dL
- Gastrointestinal bleeding, especially esophageal variceal hemorrhage
- Previous episode of SBP

Benefits of SBP Prophylaxis

- Reduction in mortality rate and bacterial infections¹³
- Cost benefit¹⁴
- Improvement in hemodynamics including elevated blood pressure and systemic vascular resistance¹⁵

SELECTED REGIMENS FOR SBP PROPHYLAXIS IN PATIENTS WITH ASCITES¹⁶

Regimen	Comment
Norfloxacin 400 mg po qd	For either short-term inpatient (7 days) or long-term outpatient use in patients with either AFTP <1 g/dL or serum bilirubin >2.5 mg/dL
Trimethoprim-sulfamethoxazole 1 DS tablet po qd, 5 days per week (Monday-Friday)	For either short-term inpatient (7 days) or long-term outpatient use in patients with either AFTP <1 g/dL or serum bilirubin >2.5 mg/dL
Norfloxacin 400 mg po bid for 7n days	For patients with variceal hemorrhage
Ofloxacin 400 mg IV qd	For use during active GI bleeding

Differentiating SBP From Secondary Bacterial Peritonitis

- Secondary bacterial peritonitis results when there is a positive ascitic fluid culture along with >250 PMN/mm³ in the ascites in the presence of a surgically treatable source of infection (i.e., perforated viscus)⁵
- Should be considered when a patient develops peritonitis while on broad spectrum antibiotics
- Other clues suggesting secondary bacterial peritonitis (high sensitivity but low specificity)⁵
 - Poor response to antibiotic therapy
 - Multiple organisms cultured from ascites (especially anaerobes or fungi)
 - PMN count >1000 per mm³
 - Two of the following three ascitic fluid parameters: glucose levels <50 mg/dL; ascitic fluid total protein >1 g/dL; lactate dehydrogenase greater than the upper limit of normal for serum
- Patients who meet any of the above criteria should undergo emergency imaging of the abdomen (flat and upright abdominal plain films versus water-soluble contrasted studies)⁵
 - Evidence of free air or contrast extravasation from the gut requires prompt surgical consult for laparotomy
 - If neither free air nor extravasation is demonstrated, perform repeat paracentesis in 48 hours of antibiotic treatment; if PMN count rises or initial culture grows multiple organisms, further investigation is warranted
- There is an 80% mortality rate for a patient with SBP who receives an exploratory laparotomy; differentiation is crucial¹⁷



Patient Care Warnings

- Have a high index of suspicion for SBP in all patients with advanced liver disease especially if they have clinical manifestations of infection; have a low threshold to perform diagnostic paracentesis
- Begin empiric antibiotics immediately without waiting for laboratory values and culture results if SBP is highly suspected
- Failure of antibiotic treatment should prompt evaluation for secondary bacterial peritonitis

References

- ② 1. Fernández J, Navasa M, Gómez J, et al. Bacterial infections in cirrhosis: Epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002;35:140-48.
- ③ 2. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: A consensus document. *J Hepatol* 2000;32:142.
- ③ 3. Such J, Runyon BA. Spontaneous bacterial peritonitis. *Clin Infect Dis* 1998;27:669-74.
- ③ 4. McHutchison JG, Runyon BA. Spontaneous bacterial peritonitis. In Surawicz CM, Owen RL (eds.), *Gastrointestinal and Hepatic Infections*. WB Saunders, Philadelphia, 1994:455.
- ② 5. Akriviadis EA, Runyon BA. Utility of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. *Gastroenterology* 1990;98:127-33.
- ② 6. Runyon BA, Antillon MR, Akriviadis EA, et al. Bedside inoculation of blood culture bottles with ascitic fluid is superior to delayed inoculation in the detection of spontaneous bacterial peritonitis. *J Clin Microbiol* 1990;28:2811-12.
- ② 7. Runyon BA, Canawati HN, Akriviadis EA. Optimization of ascitic fluid culture technique. *Gastroenterology* 1988;95:1351-55.
- ② 8. Antillon MR, Runyon BA. Effect of marked peripheral leukocytosis on the leukocyte count in ascites. *Arch Intern Med* 1991;151:509-10.

- ① 9. Felisart J, Rimola A, Arroyo V, et al. Randomized comparative study of efficacy and nephrotoxicity of ampicillin plus tobramycin versus cefotaxime in cirrhotics with severe infections. *Hepatology* 1985;5:457-62.
- ③ 10. Quenzer RW. Primary peritonitis: Spontaneous bacterial peritonitis. *Curr Treat Options Infect Dis* 2001;3:359-65.
- ① 11. Runyon BA, McHutchison JG, Antillon MR. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis: A randomized controlled study of 100 patients. *Gastroenterology* 1991;100:1737-42.
- ① 12. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403-409.
- ① 13. Soares-Weiser K, Brezis M, Tur-Kaspa R, et. al. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: A meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2003;38:193-200.
- ② 14. Inadomi J, Sonnenberg A: Cost-analysis of prophylactic antibiotics in spontaneous bacterial peritonitis. *Gastroenterology* 1997;113:1289-94.
- ① 15. Rasaratnam B, Kaye D, Jennings G, et al. The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis: A randomized trial. *Ann Intern Med* 2003;139:186-93.
- ③ 16. Runyon BA, Practice Guidelines Committee, American Association for the Study of Liver Diseases (AASLD). Management of adult patients with ascites caused by cirrhosis. *Hepatology* 2004;39:841-56.
- ② 17. Garrison RN, Cryer HM, Howard DA, et al. Clarification of risk factors for abdominal operations in patients with hepatic cirrhosis. *Ann Surg* 1984;199:648-55.

ABNORMAL LIVER FUNCTION TESTS

Classifications, Etiology, and Rationale of Liver Chemistries

- Test interpretation must start with the evaluation of patient's risk factors for disease, symptoms, and physical examination findings in order to assess the likelihood of liver disease as well as its severity and possible etiology

OVERVIEW OF LIVER CHEMISTRIES¹

Test	Clinical Significance	Extrahepatic Sources
Alanine aminotransferase (ALT)	Hepatocellular damage	Relatively specific for hepatocyte; can be elevated in myopathic disease
Aspartate aminotransferase (AST)	Hepatocellular damage	Muscle (skeletal and cardiac), red blood cells, kidney, brain, pancreas
Bilirubin	Cholestasis, impaired conjugation, evaluation of synthetic function	Increased breakdown of hemoglobin or myoglobin
Alkaline phosphatase (AP)	Cholestasis	Bone growth or disease (e.g., Paget's), placenta, intestine, tumors
Gamma glutamyl transpeptidase (GGT)	Cholestasis; can be induced by alcohol, anticonvulsants, or warfarin	Kidney, pancreas, intestine, prostate
5-Nucleotidase	Cholestasis	Relatively specific for liver disease
Prothrombin time/International Normalized Ratio (PT/INR)	Evaluation of synthetic function; best indicator of acute liver failure	Prolonged in vitamin K deficiency, disseminated intravascular coagulopathy
Albumin	Evaluation of synthetic function	Low in nephrotic syndrome, protein losing enteropathy, and malignancy

Patterns of Liver Function Test Abnormalities

- Hepatitic (predominant abnormality in AST and ALT)
- Cholestatic (predominant abnormality in AP)
- Pattern recognition is important to guide clinical evaluation, biochemical testing for disease-specific markers, imaging, and liver biopsy

- Most patients present with an overlapping pattern of abnormalities; in these cases the most relevant abnormality will lead to further workup

	AST/ALT	AP	Total Bilirubin
Hepatic	>5 ULN*	<3 ULN	1-30 ULN
Cholestatic			
Intrahepatic	<5 ULN	>3 ULN	<3 ULN*
Extrahepatic	<3 ULN	1-20 ULN	1-30 ULN

ULN: upper limit of normal

*Total bilirubin <3 ULN is seen in early chronic cholestatic disease; in advanced disease total bilirubin is higher

HEPATIC PATTERN: REFLECTS PREDOMINANT HEPATOCELLULAR INJURY¹⁻³

ALT and AST >500 IU/L (international units per liter)	Noninvasive Tests/ Diagnostic Clues
Frequent (especially associated with ALT and AST >2000 IU/L) • Drug-/toxin-induced liver injury (acetaminophen, herbs, over-the-counter medications) • Acute viral hepatitis • Hepatitis A • Hepatitis B • Hepatitis C • Hepatitis D, E • Herpes simplex virus (HSV-1 or HSV-2) • Ischemic hepatitis • Decompensated congestive heart failure • Cocaine use • Hypotension/sepsis	Detailed list of medications, course of ALT elevation (see Fig. 1) Anti-HAV IgM Anti-HBsAg, anti-HB core IgM HCV antibodies, HCV RNA viral load Anti-delta antigen and anti-HE Specific serology Lactate dehydrogenase >5000 B-type natriuretic peptide, physical examination Urine toxicology screen Clinical correlation

(Continued on following page)

HEPATIC PATTERN: REFLECTS PREDOMINANT HEPATOCELLULAR INJURY¹⁻³ (Continued)

ALT and AST >500 IU/L (international units per liter)

Noninvasive Tests/ Diagnostic Clues

Other

• Acute bile duct obstruction • Acute Budd-Chiari syndrome • Autoimmune hepatitis • Hepatic artery ligation • Acute fatty liver disease of pregnancy and HELLP	- RUQ ultrasound - Doppler ultrasound of abdomen - ANA, ASMA, anti-LKM1 - History of recent biliary surgery

ALT and AST <500 IU/L

Noninvasive Tests/ Diagnostic Clues

ALT predominant

• Chronic hepatitis C • Chronic hepatitis B • Medications/toxins/herbs • Nonalcoholic Steato-Hepatitis (NASH) • Autoimmune hepatitis • Wilson's disease • α-1 antitrypsin deficiency • Hemochromatosis • Celiac disease	- HCV antibodies, HCV RNA viral load - HBsAg, HBV DNA - List of all medications (including over-the-counter) - Liver ultrasound - ANA, ASMA, anti-LKM1 - Ceruloplasmin, 24-hour urine copper α-1 antitrypsin level - Transferrin saturation, HFE genetic test - Antiendomysial, antigliadin antibodies

AST predominant

• Alcoholic liver disease • Extrahepatic source (hemolysis, myopathy, thyroid disease, strenuous exercise)	- AST/ALT >2; AST and ALT usually <300 IU/L - Hematocrit, reticulocyte count, creatine kinase, TSH and free T4

ANA: antinuclear antibodies; ASMA: anti-smooth muscle antibodies; anti-LKM1: anti-liver kidney microsomal 1; normal AST/ALT is 1 or <1

Image rights unavailable.

Comparison of time course of ALT elevations between different causes of hepatocellular injury. (From Davern T, Scharschmidt B. Biochemical liver tests. In Feldman M, Friedman LS, Brandt LJ (eds). Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 7th ed. 2002:1227-38.)

Cholestatic Pattern¹⁻³

- The first step in the evaluation of AP is to determine whether AP is hepatic or nonhepatic in origin by measuring GGT and 5'-nucleotidase; there are two types of cholestatic patterns

Intrahepatic Cholestasis

- Characterized by a disproportionate elevation of alkaline phosphatase compared with bilirubin, AST, and ALT (all can be normal)

Extrahepatic Cholestasis

- This can be caused by partial or complete biliary obstruction; the most important tests are imaging

Etiologies	Noninvasive Tests/ Diagnostic Clues
Primary biliary cirrhosis (PBC)	Antimitochondrial antibody young female
Medications (anabolic steroids, estrogens, antipsychotic medication)	Careful medication review
Infiltrating Diseases	
• Granulomatous	Suspect in cases of isolated elevation of alkaline phosphatase
• Tuberculosis	PPD, abnormal chest x-ray
• Sarcoidosis	African-American ethnicity
• Fungal infection	
• Lymphoma	Abdominal lymphadenopathy
• Amyloidosis	Rectal biopsy/fat pad biopsy
• Metastatic malignancy	Based on suspicion of primary source
• Hepatocellular carcinoma	Alpha-fetoprotein
Hepatitis (especially alcoholic)	
Cirrhosis	

studies (ultrasound, computed tomography abdomen, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography)

- Partial: pattern of abnormal liver chemistry tests similar to those for intrahepatic cholestasis
 - Etiologies: primary sclerosing cholangitis, recurrent pyogenic cholangitis, hilar tumor (Klatskin's tumor)

- Complete: pattern is characterized by elevated conjugated bilirubin and AP (bilirubin elevation is usually more prominent than AP elevation)
 - Etiologies
 - Intrinsic: choledocolithiasis, cysts, ampullary tumor
 - Extrinsic: pancreatic tumor, duodenal tumor, lymphadenopathy

Elevated Bilirubin¹⁻³

- Elevated bilirubin is relatively common in many forms of liver disease and does not necessarily imply the presence of either cholestatic or hepatocellular disease, nor does it indicate that liver disease is present (especially in cases of isolated unconjugated hyperbilirubinemia)

Isolated Unconjugated Hyperbilirubinemia

- Gilbert's syndrome, hemolysis, resorption of a large hematoma, Crigler-Najjar syndrome, ineffective erythropoiesis

Conjugated Hyperbilirubinemia and Elevated Alkaline Phosphatase

- Any of the causes listed under extrahepatic or intrahepatic cholestasis
- Other causes that might overlap between intra- and extrahepatic cholestatic patterns: PBC, PSC, sepsis, total parenteral nutrition, intrahepatic cholestasis of pregnancy, Dubin-Johnson syndrome, Rotor's syndrome
- Elevated bilirubin, along with elevation of AST and ALT, represents hepatocellular injury
- Elevated bilirubin along with elevation in INR can indicate liver failure

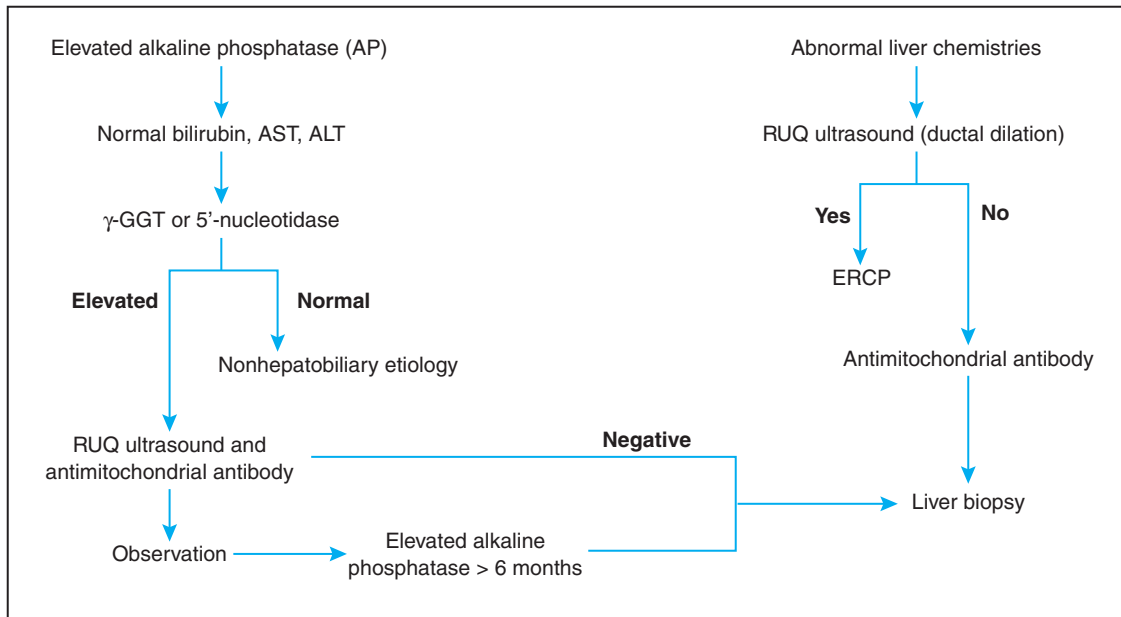


Image rights unavailable.

Selected algorithms: American Gastroenterological Association in the evaluation of cholestatic pattern. (From American Gastroenterological Association medical position statement: Evaluation of liver chemistry tests. *Gastroenterology* 2002;123:1364-67.)



Patient Care Warnings

- Albumin half-life is 20 days; not a good indicator of synthetic function in acute liver disease; PT/INR is the best
- Lactate dehydrogenase: LDH >2000 and transient elevation suggest ischemic hepatitis; sustained elevation with alkaline phosphatase elevation suggest malignant infiltration
- Of normal individuals, 2.5% will have mild elevations of a given serum chemistry test; normal test results do not ensure that patient does not have liver disease if there is a clinical suspicion

References

- ③ 1. Davern T, Scharschmidt B. Biochemical liver tests. In Feldman M, Friedman LS, Brandt LJ (eds). *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 7th ed. 2002, pp 1227-38.
- ③ 2. American Gastroenterological Association medical position statement: Evaluation of liver chemistry tests. *Gastroenterology* 2002;123:1364-67.
- ③ 3. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. *Gastroenterology* 2002;123:1367-84.

ASCITES

Definitions, Etiology, and Epidemiology

- Ascites is the most common complication of cirrhosis
 - Onset in cirrhosis indicates high risk of morbidity/mortality and should warrant consideration for liver transplantation
 - Cirrhosis (81%) and peritoneal carcinomatosis (10%) are the most common causes¹

- Causes can be categorized into portal and non-portal hypertensive ascites based on serum-ascites albumin gradient (SAAG = $\text{Albumin}^{\text{Serum}} - \text{Albumin}^{\text{Ascitic Fluid}}$) with 97% accuracy¹

CAUSES OF ASCITES	
Portal Hypertensive Ascites (SAAG ≥ 1.1)	Nonportal Hypertensive Ascites (SAAG < 1.1)
Cirrhosis	Tuberculous peritonitis (increased incidence in AIDS patients)
Alcoholic hepatitis	Pancreatic ascites
Congestive heart failure	Peritoneal carcinomatosis (usually with primary breast, colon, gastric, pancreatic cancer)
Large hepatic metastases	Nephrotic syndrome
Hepatocellular carcinoma	
Constrictive pericarditis	
Portal vein thrombosis, hepatic veno-occlusive diseases	
Transjugular intrahepatic portosystemic shunt occlusion	

Pearls of the History and Physical Examination

History

- Rapid rate of increasing abdominal girth suggests ascites rather than obesity
- Risk factors for liver disease (alcohol use, recreational drug history, travel history, viral hepatitis, emigration history [infectious etiology] and family history [genetic disorders])
- Hypercoagulable states
- History of jaundice, hepatitis, cancer, heart failure, and tuberculosis
- Recent placement of transjugular intrahepatic portosystemic shunt (TIPS)²

Physical Examination

- Bulging flanks with shifting dullness, fluid wave
- Stigmata of cirrhosis: spider angiomas, caput

madusae, evidence of hyperestrogenism (gynecomastia, testicular atrophy, palmar erythema)

Diagnostic Studies and Laboratory Values

Blood Tests

- Baseline liver function tests include serum albumin (to calculate SAAG) and total protein (see below), serum chemistries, and complete blood count (thrombocytopenia can indirectly suggest portal hypertension and hypersplenism)

Ultrasound (US)

- Can reveal cirrhosis, liver masses, and presence of ascites; can also help localize pockets of fluid for paracentesis
- Color flow Doppler can document portal hypertension and/or portal vein thrombosis
- TIPS patency can be also assessed,^{3,4} although a double-blind study suggested US is less sensitive than venography⁵

Ascitic Fluid Analysis (From Diagnostic Paracentesis)

ROUTINE TESTS FOR ALL SAMPLES

Test	Comments
Cell count and differential	• ≥ 250 PMNs/mm³ suggests spontaneous bacterial peritonitis (SBP) (see section titled Spontaneous Bacterial Peritonitis) • Lymphocytic pleocytosis suggests tuberculosis⁶
Albumin	• Subtracted from serum albumin level to calculate SAAG
Total protein (TP)	• TP <1 g/dL suggests need for SBP prophylaxis
Bacterial culture	• Diagnostic yield increases 50%–>80% when blood culture bottles are inoculated at bedside⁷

SUPPLEMENTARY TESTS TO BE SENT IN THE APPROPRIATE CLINICAL SETTING

Test	Comments
Cytology	97% of patients with peritoneal carcinomatosis have positive cytology results when three samples are sent⁸
Gram's stain	Be judicious when sending Gram's stain: organism counts are typically too low for detection; additionally, Gram's stain with negative culture result may muddy the clinical picture
Triglycerides	- Should be assessed when milky ascites is present - Levels >200 mg/dL suggest chylous ascites (from lymphatic trauma or obstruction after abdominal surgery, malignancy, cirrhosis)⁹
Acid-fast bacillus (AFB) culture	- Sensitivity ~50% for tuberculous peritonitis¹⁰ - Do not order AFB smear as sensitivity ~0%¹⁰
Adenosine Deaminase	- Used to detect tuberculous peritonitis - Sensitivity much lower in cirrhotic (30%)¹¹ than noncirrhotic patients (100%)¹²
Amylase	Levels > 2000 IU/L suggest pancreatitis¹³
Bilirubin	- Should be measured if ascites is brown - Elevations greater than serum levels suggest bowel or biliary perforation

Guide to Acute Management

- If patient already has a TIPS (see below), assess for occlusion and consult interventional radiology if occluded

Diagnostic Paracentesis

- Indications for paracentesis: new-onset ascites, worsening ascites, suspected SBP (fever, abdominal pain, altered mental status, acidosis, gastrointestinal bleed with ascites present, etc.)
- Send fluid for appropriate studies as above

- Postparacentesis bleeding that requires transfusion is rare, so prophylactic transfusion of plasma/platelets is not recommended even when there is a significant coagulopathy¹⁰

Intake Restrictions¹⁰

- Sodium restriction (2 g/d [88 mmol/d]); fluid restriction only if serum sodium <120-125 mmol/L
- Cessation of alcohol

Diuretics¹⁰

- Initially 100 mg po spironolactone and 40 mg po furosemide daily
 - Titrate every 3-5 days with attempted preservation of 100:40 spironolactone-to-furosemide ratio to maintain normokalemia
 - Maximum dose: 400 mg spironolactone daily and 160 mg furosemide daily
- Monotherapy with spironolactone not recommended due to increased risk of hyperkalemia
- Follow daily weights: no limit on weight loss until peripheral edema resolved, then 0.5 kg/d
- Follow daily fluid intake and output: peritoneum cannot absorb more than 300-500 mL ascites daily
- Goal with diuretic patients is to increase urinary excretion of sodium to >78 mmol/d (restricted intake of 88 mmol/d – 10 mmol/d of nonurinary sodium loss); water follows sodium excretion
 - Monitor urine Na and urine K daily; spot urine Na > urine K suggests urine sodium excretion 78 mmol/d with 90% accuracy when compared with 24-hour urine Na levels¹⁴
- When initiating diuresis, check daily chemistries including blood urea nitrogen and creatinine
- Stable patients who are responding to treatment may be discharged with outpatient follow-up within 1 week even if there is evidence of more volume

Large-Volume Paracentesis

- Indicated for tense ascites or if patient is uncomfortable/dyspneic; a single paracentesis removing 5 L of fluid can safely be done without colloid infusion¹⁰
- Larger volumes can be removed with concurrent infusion of albumin (8 g/L of fluid removed)

Refractory Ascites

- Occurs in ~10% of patients with ascites¹⁰
- May require further interventions such as serial paracenteses and TIPS



Patient Care Warnings

- Paracentesis and ascitic fluid analysis must be done immediately for any patient with new-onset ascites and whenever infection is suspected; US guidance can be useful when fluid is difficult to define
- Large-volume paracentesis can be performed safely if symptoms warrant rapid removal of fluid
- Follow daily serum chemistries when initiating diuresis to monitor for electrolyte abnormalities and renal failure

References

- ② 1. Runyon BA, Montano AA, Akriviadis EA, et al. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med* 1992;117:215-20.
- ② 2. Sanyal AJ, Freedman AM, Luketic VA, et al. The natural history of portal hypertension after transjugular intrahepatic portosystemic shunts. *Gastroenterology* 1997;112:889-98.
- ① 3. Kanterman RY, Darcy MD, Middleton WD, et al. Doppler

sonography findings associated with transjugular intrahepatic portosystemic shunt malfunction. *Am J Roentgenol* 1997; 168:467-72.

- ① 4. Dodd GD, Zajko AB, Orons PD, et al. Detection of transjugular intrahepatic portosystemic shunt dysfunction: Value of duplex Doppler sonography. *Am J Roentgenol* 1995; 164:1119-24.
- ① 5. Owens CA, Bartolone C, Warner DL, et al. The inaccuracy of duplex ultrasonography in predicting patency of transjugular intrahepatic portosystemic shunts. *Gastroenterology* 1998;114:975-80.
- ③ 6. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. *Am J Gastroenterol* 1993;88:989-99.
- ② 7. Runyon BA, Antillon MR, Akriviadis EA, et al. Bedside inoculation of blood culture bottles with ascitic fluid is superior to delayed inoculation in the detection of spontaneous bacterial peritonitis. *J Clin Microbiol* 1990;28:2811-12.
- ② 8. Runyon BA, Hoefs JC, Morgan TR. Ascitic fluid analysis in malignancy-related ascites. *Hepatology* 1988;8:1104-09.
- ② 9. Press OW, Press NO, Kaufman SD. Evaluation and management of chylous ascites. *Ann Intern Med* 1982;96:358-64.
- ③ 10. Runyon BA, Practice Guidelines Committee, American Association for the Study of Liver Diseases (AASLD). Management of adult patients with ascites caused by cirrhosis. *Hepatology* 2004;39:841-56.
- ② 11. Hillebrand DJ, Runyon BA, Yasmineh WG, et al. Ascitic fluid adenosine deaminase insensitivity in detecting tuberculous peritonitis in the United States. *Hepatology* 1996; 24:1408-12.
- ② 12. Voigt MD, Kalvaria I, Trey C, et al. Diagnostic value of ascites adenosine deaminase in tuberculous peritonitis. *Lancet* 1989;1:751-54.
- ② 13. Runyon BA. Amylase levels in ascitic fluid. *J Clin Gastroenterol* 1987;9:172-74.
- ③ 14. Stiehm AJ, Mendler MH, Runyon BA. Detection of diuretic-resistance or diuretic-sensitivity by spot urine Na/K ratios in 729 specimens from cirrhotics with ascites: Approximately 90 percent accuracy as compared to 24-hr urine Na excretion [abstract]. *Hepatology* 2002;36:222A.

ACUTE VIRAL HEPATITIS

Definition, Etiology, and Epidemiology

- See section titled Acute Liver Failure if clinical scenario dictates (altered mentation, coagulopathy

defined as prothrombin time > 4 seconds or international normalized ratio > 1.5)

- Five known causes: hepatitis A, B, C, D (or delta), and E

Hepatitis A (HAV)

- Infection occurs worldwide; caused by a picornavirus identified in 1973¹
- Transmitted by fecal-oral route (person-person, or food contamination), not by saliva or urine²
- Risk factors: unknown (48%), international travel (5%), intravenous drug addiction (IVDA) (5%), males who have sex with males (MSM; 10%), day care (8%), household or sexual contacts (14%), common source outbreak (4%), other contact (8%)³
- HAV contamination from a food product can occur at any point during the product's cultivation, harvesting, processing, distribution, or preparation
- Children can be asymptomatic; adults may present anywhere from a flulike illness to acute liver failure (ALF), and there is no carrier state; incubation is about 2-4 weeks

Hepatitis B (HBV)

- Derives from *Hepadnaviridae*, a double-stranded DNA virus
- Transmitted via blood or bodily fluids of infected individuals and from mother to child at birth
- Risk factors: multiple sex partners, MSM, IVDA, immigrants from endemic areas, health care and public safety workers, and hemodialysis patients
- 30% develop icterus; disease severity greater with underlying liver disease⁴; incubation period 1-4 months; some may progress to ALF (more than hepatitis A); there is a chronic carrier state in 5% after acute hepatitis in adults (with consequences of cirrhosis and hepatocellular carcinoma, presumably due to genotoxic effect of HBV DNA to host DNA)^{5,6}

Hepatitis C (HCV)

- Acute infection rarely causes ALF
- Most common blood-borne infection in the United States (1.8% of population); 40% of chronic liver disease due to HCV; most affected people are unaware because of lack symptoms in the acute phase⁷
- Transmitted via blood or bodily fluids of infected individuals and perinatally
- Acute infection (commonly leads to chronic infection 60%-80% of cases) symptoms are similar to those of other forms of hepatitis, occurring after an incubation of 5-10 weeks, peak of 7-8 weeks
- Cirrhosis develops in 50% of patients, with the most common complication being ascites
- Risk factors: IVDA,⁸ blood transfusion or organ transplant prior to July 1992,⁹ multiple sex partners,¹⁰ perinatal transmission, hemodialysis, health-care workers, recipients of clotting factors before 1987,¹¹ history of body art (tattooing or piercing)

Hepatitis D (HDV, Delta Antigen)

- Defective virus requiring presence of HBV because simultaneous presence is needed to execute successful replication; infection may occur as:
 - Coinfection: acute HBV/HDV, which is clinically indistinguishable from acute HBV
 - Superinfection: HDV infects HBsAg carrier, resulting in exacerbation of chronic HBV or severe acute hepatitis in a clinically silent carrier; progression to chronic HDV is common¹²
- Transmitted via blood or bodily fluids of infected individuals and perinatally
- Risk factors: IVDA, MSM, hemodialysis, health-care workers, sex with infected persons
- ALF more common than in HBV infection alone

Hepatitis E (HEV)

- First documented in New Delhi, India, 1955¹³
- Found in feces of infected individuals; transmission by contamination of food sources^{14,15}; person-to-person transmission is uncommon, no carrier state, and up to 6 weeks incubation period¹³
- More severe in third trimester of pregnancy^{16,17}

Pearls of the History and Physical Examination

History

- Directed history: sexual, international travel, food ingestion, blood transfusions, IVDA
- Symptoms: jaundice, fatigue, malaise, nausea, vomiting, anorexia, fever, right upper quadrant pain,¹⁸ and smokers report losing the desire to smoke
- Hepatitis A,D,E: dark urine and acholic stools
- Hepatitis B: serum sickness–like illness prior to jaundice onset: fever; skin rashes; arthralgia and arthritis, which may subside
- Hepatitis C: in acute state absent or protean symptoms; in chronic state fatigue is most common complaint; important extrahepatic manifestations include¹⁹:
 - Hematological disease: essential mixed cryoglobulinemia (presents with arthralgias, weakness, and palpable purpura)
 - Renal disease: commonly membranoproliferative glomerulonephritis and occasionally membranous nephropathy (therefore may present with nephrotic syndrome)
 - Dermatological disease: lichen planus (LP), vitiligo, and porphyria cutanea tarda (PCT)
- Hepatitis D: mainly follows IVDA, either simultaneous coinfection or superinfection of previous HBsAg carrier; no extrahepatic diseases recognized.

Physical Examination

- Common findings: icterus, jaundice, hepatomegaly, skin rashes
- Extrahepatic manifestations of HCV: PCT (photosensitivity, skin fragility, bruising, and hemorrhagic bullae), LP (flat, violaceous, pruritic papules), vitiligo (skin depigmentation)

Diagnostic Studies and Laboratory Values

Blood Tests

- Aminotranferase, total/direct bilirubin, alkaline phosphatase elevation
- Hepatitis A: alanine aminotransferase (ALT) > aspartate aminotransferase (AST) (>1000 IU/dL), IgM HAV antibody gold standard for acute diagnosis (positive at symptom onset and 4-6 months thereafter)
- Hepatitis B: ALT > AST (>1000-2000 IU/L)

	Acute		Chronic	
	Early (~≤4 months)	<6 months	Cleared HBV (>6 months)	(>6 months)
HBsAg	+	—	—	+
Anti HBc IgM ²⁰	+	+	—	—
Total anti-HBc	+	+	+	+
Anti-HBs	—	—/+	+	—

- Hepatitis C: with appropriate risk factors and a positive anti-HCV result, a diagnosis can be made; confirm with HCV RNA if any doubt exists
 - Acute infection: HCV Ab is detectable 8 weeks after exposure, whereas HCV RNA is detectable within 2 weeks
 - Immunosuppressed or decreased antibody pro-

duction states: transplant recipients, HIV, and chronic hemodialysis²¹

- Hepatitis D: due to the dependence of HDV on HBV, the diagnosis of HDV cannot be made without markers of HBV
- Hepatitis E: IgM HEV antibody

	Acute HBV/ HDV Coinfection	Acute HDV Superinfection	Chronic HDV Infection
HBsAg	+	+	+
IgM HBcAb	+	—	—
HD Ag	+ (transient)	+ (early, transient)	—
HDV RNA	+ (transient)	+ (early, persistent)	+
IgM HDV Ab	+ (transient)	+	Variable
Total HDV Ab	+	+	+

Guide to Acute Management

- Referral to a liver specialist is best when chronic disease is discovered

Hepatitis A

- Infection is always self-limited, but ALF can occur in the elderly, those using acetaminophen, and those with underlying liver disease (e.g., hepatitis B or C)²²⁻²⁴; therefore, treatment is supportive
- Pre-exposure prophylaxis: intramuscular (IM) injection of pooled serum immune globulin (0.06 mL/kg) provides up to 6 months of immunity if administered 2 weeks prior to exposure
 - HAV vaccine (HAVRIX 1440 EL U/mL, 1 mL IM), licensed in 1995 for patients ≥ 2 years of age, with a booster at 6 months²⁵⁻²⁷
 - Indications: children in endemic areas, MSM, IVDA, travelers to endemic areas, occupations at risk, those with clotting factor disorders, and those with chronic liver disease

- Postexposure prophylaxis: if patient is in a high-risk group (as above) for repeated exposure, simultaneous administration at different sites of vaccine and serum immune globulin may be warranted (0.02 mL/kg)²⁶

Hepatitis B

- Complete recovery occurs in >90% of patients (a result of host immune system versus virus interplay); therefore, therapy is mainly supportive; for management of HBV-related ALF; see section titled Acute Liver Failure
- Progression to chronic hepatitis is <5% for adult-acquired HBV²⁸
- Treatment is mainly for chronic HBV and includes interferon- α (IFN- α), lamivudine, adefovir, and entecavir
- Pre-exposure prophylaxis: with HBV vaccine for high-risk groups (neonates, individuals with multiple sex partners, IVDA, household contacts of patients with HBV, health-care workers, chronic hemodialysis)
 - Engerix-B 1.0 mL (20 μ g) or Recombivax-HB 1.0 mL (10 μ g) at 0, 1, 6 months (0.5 mL for pediatric dosing)
- Postexposure prophylaxis (including neonates born to HBsAg-positive mothers): administer vaccination (within 12 hours of birth or exposure) and 2 doses of hepatitis B immune globulin (0.06 mL/kg) 1 month apart

Hepatitis C

- Postexposure prophylaxis: there are no data to support use of IFN or immunoglobulin as post-exposure prophylaxis; needle sticks should be followed expectantly with testing through 6 months

postexposure but likelihood of infection is $<4\%$; if acute infection develops, it can be treated successfully in $>0.5\%$ of cases; current mainstays of therapy are pegylated-interferon ($\alpha 2a$ and $\alpha 2b$) and ribavirin; early detection of chronic state and referral for treatment are recommended

- A theoretical argument can be made to start treatment when HCV RNA becomes detectable and perhaps prevent progression to chronic state
- Non-United States studies using various regimens and subjects with peak ALT levels 500-1,000 IU/L when therapy was initiated (2-4 months after exposure) demonstrated that a short course of IFN started early in acute infection is associated with a higher rate of resolved infection than when therapy is initiated when disease is well established^{29,30}
- No optimal regimen has been established, but in the above studies daily doses of 6 or 10 million units daily of IFN- α 2b or IFN- β produced better responses at follow-up
- Complete recovery occurs in $<15\%$ of patients and most likely to be observed in 12 weeks after symptom onset; as high as 50% resolution in those developing symptoms (seeking evaluation due to jaundice, etc); subsequent determinations of clearance (HCV RNA status) should be done at 3-month intervals; if positive results >4 -6 months, consider treatment of acute disease

Hepatitis D

- Prevention³¹
 - HBV-HDV coinfection: pre- or postexposure prophylaxis to prevent HBV infection (above)
 - HBV-HDV super-infection: education to avoid contracting HDV
 - HDV vaccine has been tested only in animals³²

- Treatment: supportive care for acute infection; for chronic infection, IFN- α has been approved; success rate is low but early therapy initiation is recommended for chronic hepatitis (ALT elevation) with active liver disease on biopsy with IFN- α to be done at a referral center

Hepatitis E

- Supportive care; no proven vaccines or role for immune serum immunoglobulin³³



Patient Care Warnings

- Extrahepatic manifestations of chronic HBV include polyarteritis nodosa, membranous nephropathy, and membranoproliferative glomerulonephritis
- Essential mixed cryoglobulinemia is an indication for treatment of HCV

References

- ③ 1. Feinstone SM, Kapikian AZ, Purcell RH. Hepatitis A: Detection by immune electron microscopy of a virus-like antigen associated with acute illness. *Science* 1973;182:1026.
- ② 2. Staes CJ, Schlenker TL, Risk I, et al. Sources of infection among persons with acute hepatitis A and no identified risk factors during a sustained community-wide outbreak. *Pediatrics* 2000;106:E54.
- ③ 3. Centers for Disease Control and Prevention. Hepatitis surveillance report no. 57. Atlanta: Centers for Disease Control and Prevention, 2000.
- ② 4. Liaw YF, Chien RN, Chen TJ, et al. Concurrent hepatitis C virus and hepatitis delta virus superinfection in patients with chronic hepatitis B virus infection. *J Med Virol* 1992;37:294-97.
- ③ 5. Michielsen PP, Francque SM, van Dongen JL. Viral hepatitis and hepatocellular carcinoma. *World J Surg Oncol* 2005;3:27.

- ② 6. Ozkal P, Ilgin-Ruhi H, Akdogan M, et al. The genotoxic effects of hepatitis B virus to host DNA. *Mutagenesis* 2005; 20:147-50.
- ③ 7. Williams I. Epidemiology of hepatitis C in the United States. *Am J Med* 1999;107:2S-9S.
- ③ 8. Alter MJ. Prevention of spread of hepatitis C. *Hepatology* 2002;36(Suppl 1):S93-98.
- ② 9. Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections: The Retrovirus Epidemiology Donor Study. *N Engl J Med* 1996;334:1685-90.
- ② 10. Lissen E, Alter HJ, Abad MA, et al. Hepatitis C virus infection among sexually promiscuous groups and the heterosexual partners of hepatitis C virus-infected index cases. *Eur J Clin Microbiol Infect Dis* 1993;12:827-31.
- ② 11. Soucie JM, Richardson LC, Evatt BL, et al. Risk factors for infection with HBV and HCV in a large cohort of hemophilic males. *Transfusion* 2001;41:338-43.
- ② 12. Smedile A, Dentico P, Zanetti A, et al. Infection with the delta agent in chronic HBsAg carriers. *Gastroenterology* 1981;81:992-97.
- ② 13. Gupta DN, Smetana HF. The histopathology of viral hepatitis as seen in the Delhi epidemic (1955-56). *Indian J Med Res* 1957;45:101.
- ② 14. Khuroo MS. Study of an epidemic of non-A, non-B hepatitis: Possibility of another human hepatitis virus distinct from post-transfusion non-A, non-B type. *Am J Med* 1980;68: 818-24.
- ② 15. Naik SR, Aggarwal R, Salunke PN, et al. A large waterborne viral hepatitis E epidemic in Kanpur, India. *Bull World Health Organ* 1992;70:597-604.
- ② 16. Asher LV, Innis BL, Shrestha MP, et al. Virus-like particles in the liver of a patient with fulminant hepatitis and antibody to hepatitis E virus. *J Med Virol* 1990;31:229-33.
- ② 17. Tsaga E, Hansson BG, Krawczynski K, et al. Acute sporadic viral hepatitis in Ethiopia: Causes, risk factors, and effects on pregnancy. *Clin Infect Dis* 1992;14:961-65.
- ③ 18. Lednar WM, Lemon SM, Kirkpatrick JW, et al. Frequency of illness associated with epidemic hepatitis A virus infections in adults. *Am J Epidemiol* 1985;122:226-33.
- ② 19. El-Serag HB, Hampel H, Yeh C, et al. Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology* 2002;36:1439-45.
- ③ 20. Cohen BJ. The IgM antibody responses to the core antigen of hepatitis B virus. *J Med Virol* 1978;3:141-49.
- ③ 21. Pawlotsky JM. Use and interpretation of virological tests for hepatitis C. *Hepatology* 2002;36(Suppl 1):S65-73.
- ② 22. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *New Engl J Med* 1998;338:286-90.
- ③ 23. Vento S. Fulminant hepatitis associated with hepatitis A virus

- superinfection in patients with chronic hepatitis C. *J Viral Hepatol* 2000;7(Suppl 1):7-8.
- ② 24. Pramoolsinsap C, Poovorawan Y, Hirsch P, et al. Acute hepatitis-A super-infection in HBV carriers, or chronic liver disease related to HBV or HCV. *Ann Trop Med Parasitol* 1999;93:745-51.
 - ① 25. Innis BL, Snitbhan R, Kunasol P, et al. Protection against hepatitis A by an inactivated vaccine. *JAMA* 1994;271:1328-34.
 - ③ 26. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1999;48:1-37.
 - ③ 27. Clemens R, Safary A, Hepburn A, et al. Clinical experience with an inactivated hepatitis A vaccine. *J Infect Dis* 1995;171:S44-49.
 - ② 28. Tassopoulos NC, Papaevangelou GJ, Sjogren MH, et al. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology* 1987;92:1844-50.
 - ① 29. Vogel W, Graziadei I, Umlauf F, et al. High-dose interferon- α 2b treatment prevents chronicity in acute hepatitis C: A pilot study. *Dig Dis Sci* 1996;41(Suppl 12):81S-85S.
 - ① 30. Quin JW. Interferon therapy for acute hepatitis C viral infection: A review by meta-analysis. *Aust N Z J Med* 1997;27:611-17.
 - ③ 31. <http://www.cdc.gov/ncidod/diseases/hepatitis/d/fact.htm>
 - ③ 32. Eckart MR, Dong C, Houghton M, et al. The effects of using recombinant vaccinia viruses expressing either large or small HDag to protect woodchuck hepadnavirus carriers from HDV superinfection. *Prog Clin Biol Res* 1993;382:201-205.
 - ① 33. Khuroo MS, Dar MY. Hepatitis E: Evidence for person-to-person transmission and inability of low-dose immune serum globulin from an Indian source to prevent it. *Indian J Gastroenterol* 1992;11:113-16.

BILIARY DISEASE

Extrahepatic Cholestasis

Definition, Etiology, and Epidemiology

- Intrinsic or extrinsic obstruction of the common bile duct (CBD)

ETIOLOGIES

Gallstones (choledocholithiasis)	Ampullary carcinoma
Cholangiocarcinoma	Pancreatic cancer
Biliary cyst	Hepatocellular carcinoma
Progressive sclerosing cholangitis	Metastatic tumors
Stricture	Lymphadenopathy
Parasitic infiltration	

Pearls of the History and Physical Examination***History***

- Right upper quadrant pain, jaundice, pruritis, diarrhea, acholic stools, and dark urine
- May present as ascending cholangitis or biliary pancreatitis
- With history of recent weight loss, odds ratio 17 times greater for malignancy

Physical Examination

- Usually normal, jaundice, and right upper quadrant tenderness

Diagnostic Studies and Laboratory Values***Blood Tests***

- Total and direct bilirubin, alkaline phosphatase, transaminases, and white blood cell count

Radiographic Studies

- Right upper quadrant ultrasound (US); 50% sensitive in detection of CBD stones; up to 90% sensitive in detection of CBD dilation¹
- Computed tomography (CT) scan: superior to US in detection of CBD stones and helpful in evaluating for extrinsic compression of CBD

- Endoscopic ultrasound (EUS): 95% sensitive, 95% specific for choledocholithiasis²
- Endoscopic retrograde cholangiopancreatography (ERCP): gold standard³
- Magnetic resonance cholangiopancreatography (MRCP)
- Cholangiography (surgical/percutaneous)

Guide to Acute Management

- ERCP: CBD obstruction, stone extraction, papillotomy, sphincterotomy, stent placement⁴
- Cholecystectomy to follow if obstruction is due to choledocholithiasis
- Cholecystectomy if gallstones are the cause
- Extracorporeal shock-wave lithotripsy⁵ or intraductal lithotripsy for refractory stones
- Intravenous (IV) antibiotics if evidence exists for cholangitis (see the next section Ascending Cholangitis)



Patient Care Warnings

- Complications: ascending (bacterial) cholangitis, biliary pancreatitis

Ascending Cholangitis

Definition, Etiology, and Epidemiology

- Biliary bacterial infection proximal to CBD obstruction.

- Any etiology of CBD obstruction can be complicated by cholangitis, although 85% of cases are due to choledocholithiasis⁶
- The most commonly cultured organisms are: *Escherichia coli*, *Klebsiella*, *Pseudomonas*, enterococci, and *Proteus*; 15% of infections are anaerobic

Pearls of the History and Physical Examination

History

- Clinical evidence of biliary obstruction, fever, chills, abdominal pain
- Fever, abdominal pain, and jaundice: Charcot's triad (present in 70% of patients)
- Reynold's pentad: Charcot's triad, altered mental status, and hypotension⁷

Physical Examination

- Fever (95%), right upper quadrant abdominal tenderness (90%), jaundice (80%), peritoneal signs (15%), altered mental status, shock or hemodynamic collapse

Diagnostic Studies and Laboratory Values

Blood Tests

- Bilirubin (>2 in 80% of cases), alkaline phosphatase, transaminases, white blood cell count (elevated in 80% of cases), blood cultures

Radiographic Studies

- Right upper quadrant ultrasound for CBD dilation and stones (80%-90% sensitive; may miss small stones and early obstruction)¹
- ERCP: establish and confirm diagnosis and definitive management
- Should not be delayed in cases of Charcot's triad

- MRCP: as accurate as ERCP in the diagnosis of choledocholithiasis⁸
- CT scan

Guide to Acute Management

Antibiotics

- Primarily cover gram-negative bacteria and enterococcus
- Levofloxacin 250-500 mg IV daily (add metronidazole for patients with Reynold's pentad)
- Ampicillin 2 g IV every 4 hours, with gentamicin 4-6 mg/kg IV daily
- Alternate: imipenem or Zosyn at standard dosing
- 80% of patients respond to conservative measures and IV antibiotics within 6-12 hours; biliary drainage can then be performed electively
- Note: only fluoroquinolones penetrate effectively into an obstructed bile duct compared with the other antibiotics

Urgent Biliary Decompression⁵

- Indications
 - Persistent abdominal pain
 - Persistent fever $>39^{\circ}\text{C}$
 - Persistent hypotension despite aggressive volume resuscitation
 - Altered mental status
 - ERCP with sphincterotomy: modality of choice⁹
 - Other options include percutaneous drainage and surgical decompression



Patient Care Warnings

- Complications: sepsis

Cholelithiasis and Microlithiasis (Sludge)

Definition, Etiology, and Epidemiology

- Stones in the gallbladder: microlithiasis is the presence of granules, crystals, and glycoproteins in the gallbladder; microlithiasis and cholelithiasis have a similar natural history
- Risk factors: increasing age, female gender, obesity, pregnancy, diabetes, rapid weight loss, total parenteral nutrition, inflammatory bowel disease, cirrhosis, oral contraception, and hormone replacement therapy
- Composition: cholesterol stones (75%), pigment (bilirubin) stones (10%-25%)

Pearls of the History and Physical Examination

History

- Asymptomatic in >75% of patients
- Biliary colic: postprandial right upper quadrant or epigastric abdominal pain associated with nausea, vomiting, diaphoresis, and right subscapular pain (referred)

Physical Examination

- Right upper quadrant tenderness
- Usually afebrile and nontoxic appearance

Diagnostic Studies and Laboratory Values

Blood Tests

- Usually normal evaluation

Radiographic Studies

- Right upper quadrant US: 95% sensitive for stones larger than 2 mm¹
- CT scan

Guide to Acute Management

- No treatment indicated in asymptomatic disease
- Laparoscopic cholecystectomy in symptomatic uncomplicated disease¹⁰
- Pharmacological dissolution with ursodeoxycholic acid in patients who are poor surgical candidates¹¹
- Gallbladder sludge: sphincterotomy, cholecystectomy, and dissolution therapy are effective



Patient Care Warnings

- Complications: acute cholecystitis, chronic cholecystitis, choledocholithiasis, ascending cholangitis, biliary pancreatitis, cholecystenteric fistula, gallstone ileus, gallbladder cancer

Cholecystitis

Definition, Etiology, and Epidemiology

- Inflammation of the gallbladder
- Prolonged impaction of gallstone or sludge in cystic duct in 90% of cases; 10% not associated with stones (termed acalculous cholecystitis)

Pearls of the History and Physical Examination

History

- Unrelenting right upper quadrant pain and midepigastria tenderness
- Murphy's sign: pain and inspiratory arrest with palpation of right upper quadrant during inspiration
- Right subscapular pain
- Nausea and vomiting

Physical Examination

- Fever
- Right upper quadrant pain and jaundice

Diagnostic Studies and Laboratory Values

Blood Tests

- Complete blood count: leukocytosis with left shift
- Serum chemistries: mild transaminitis, hyperbilirubinemia, and alkaline phosphatase elevation, even without CBD obstruction¹²
- Evidence of frank biliary obstruction due to cholelithiasis or cystic duct edema with resultant biliary obstruction (bilirubin >4 usually suggests concomitant CBD obstruction)¹³

Radiographic Studies

- Right upper quadrant US (88% sensitive and 80% specific)¹
 - Gallstones, thickened gallbladder wall >4 mm, and pericholecystic fluid; sonographic Murphy's sign has a $>90\%$ positive predictive value when stones are seen¹⁴
- Hepatobiliary iminodiacetic acid (HIDA) scan (97% sensitive and 90% specific)^{1,15}

- Second diagnostic step for patients with high clinical suspicion and gallstones but no other sonographic evidence of acute cholecystitis or no stones with sonographic evidence
- Specificity decreases in critically ill patients
- CT scan
 - Although diagnostically very effective, usually unnecessary unless looking for complications of cholecystitis or excluding other etiologies of abdominal pain

Guide to Acute Management

- Intravenous antibiotics: unconvincing evidence but are probably warranted in toxic-appearing patients and those with suspected complications¹⁶
- Laparoscopic cholecystectomy during hospital admission in low-to-moderate risk surgical candidates¹⁷
- Cholecystostomy or percutaneous drain in patients at high surgical risk who do not respond to conservative management^{18,19}
- CBD imaging for patients with evidence of obstruction
- Cholecystitis can also be drained transpapillary via ERCP and is useful if the patient is pancytopenic or thrombocytopenic or when percutaneous drainage is more dangerous



Patient Care Warning

- Complications: emphysematous cholecystitis, perforation with peritonitis, empyema, cholecystenteric fistula, gallstone ileus

References

- ① 1. Shea J, Berlin J, Escarce J, et al. Revised estimates of diagnostic test sensitivity and specificity in suspected biliary tract disease. *Arch Intern Med* 1994;154:2573.
- ① 2. Amouyal P, Amoutal G, Levy P, et al. Diagnosis of choledocholithiasis by endoscopic ultrasonography. *Gastroenterology* 1994;106:1062.
- ③ 3. Ott D, Gilliam J, Zagoria, et al. Interventional endoscopy of the biliary and pancreatic ducts: Current indications and methods [review]. *Am J Roentgenol* 1992;159:243.
- ③ 4. Cotton P. Endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy [review]. *Am J Surg* 1995;165:474.
- ③ 5. Garcia G, Young HS. Biliary extracorporeal shock-wave lithotripsy. *Gastroenterol Clin North Am* 1991;20:201.
- ③ 6. Pitt H, Cameron J. Acute cholangitis. In Way L, Pellegrini C. *Surgery of the Gallbladder and Bile Ducts*. Philadelphia, WB Saunders, 1987, p 295.
- ③ 7. DenBesten L, Doty JE. Pathogenesis and management of cholelithiasis. *Surg Clin North Am* 1981;61:893.
- ① 8. Chan YL; Chan AC; Lam WW; et al. Choledocholithiasis: Comparison of MR cholangiography and endoscopic retrograde cholangiography. *Radiology* 1996;200:85.
- ③ 9. Cotton P. Endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy [review]. *Am J Surg* 1995;165:474.
- ③ 10. Lee V, Chari R, Cucchiaro G, et al. Complications of laparoscopic cholecystectomy [review]. *Am J Surg* 1993; 165: 527.
- ② 11. Tomida S, Abei M, Yamaguchi T, et al. Long-term ursodeoxycholic acid therapy is associated with reduced risk of biliary pain and acute cholecystitis in patients with gallbladder stones: A cohort analysis. *Hepatology* 1999;30:6.
- ② 12. Kurzweil SM, Shapiro MJ, Andrus CH, et al. Hyperbilirubinemia without common bile duct abnormalities and hyperamylasemia without pancreatitis in patients with gallbladder disease. *Arch Surg* 1994;129:829.
- ③ 13. Dumont, A. Significance of hyperbilirubinemia in acute cholecystitis. *Surg Gyn Obstet* 1976;142:855.
- ① 14. Ralls P, Colletti P, Lapin S. Real-time sonography in suspected acute cholecystitis. *Radiology* 1985;155:767.
- ① 15. Fink-Bennett D; Freitas JE; Ripley SD; et al. The sensitivity of hepatobiliary imaging and real-time ultrasonography in the detection of acute cholecystitis. *Arch Surg* 1985; 120:904.
- ③ 16. Runyon B. Ascites and spontaneous bacterial peritonitis. In Feldman M, Scharschmidt BF, Sleisenger H (eds). *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 6th ed. Philadelphia, WB Saunders, 1998:1310-33.

- ① 17. Lujan J, Parrilla P, Robles R, et al. Laparoscopic cholecystectomy in the treatment of acute cholecystitis. *J Am Coll Surg* 1995;181:75.
- ② 18. Melin MM, Sarr MG, Bender CE, et al. Percutaneous cholecystostomy: A valuable technique in high-risk patients with presumed acute cholecystitis. *Br J Surg* 1995;82:1274.
- ③ 19. Byrne MF, Suhocki P, Mitchell RM, et al. Percutaneous cholecystostomy in patients with acute cholecystitis: Experience of 45 patients at a US referral center. *J Am Coll Surg* 2003;197:206.

ESOPHAGEAL DISORDERS

Dysphagia

Definition, Etiology, and Epidemiology

- Perception that there is an impediment to the normal passage of swallowed material
- It can be caused by a number of disorders, benign and malignant, that involve either the oropharynx or the esophagus¹
- Etiologies vary with age, sex, and race; for example, cerebrovascular accidents are frequent causes of oropharyngeal dysphagia in elderly patients with a history of atherosclerotic disease
- Transfer (oropharyngeal) dysphagia can be secondary to propulsive failure or structural abnormalities in the upper esophagus or pharynx
 - Propulsive failure can result from dysfunction of central nervous system control mechanisms, intrinsic musculature, or peripheral nerves²
 - Structural abnormalities may result from neoplasm, surgery, trauma, caustic injury, or congenital abnormalities
- Etiology of esophageal dysphagia can be subclassified into structural (mechanical obstruction) or func-

tional (motility disorder), both of which frequently require further testing

- No particular age, sex, or race in which dysphagia is predominantly present

Pearls of the History and Physical Examination

History

- Distinguish between transfer (difficulty transferring food from the oropharynx to the esophagus) and esophageal (difficulty getting food down the esophagus into the stomach) dysphagia
- Patients with oropharyngeal disorders may experience difficulty in initiating a swallow, and swallowing may be accompanied by nasopharyngeal regurgitation, pulmonary aspiration, and a sensation that residual material remains in the pharynx; if any of these symptoms are prominent, evaluation for oropharyngeal dysfunction may precede tests for esophageal disorders
- Time course of the dysphagia (progressive or intermittent)
- Difficulty with solids > liquids indicates structural process (i.e., obstruction)³
- Difficulty with solids and liquids usually functional problem (i.e., motility disorder)³
- Associated symptoms (weight loss, focal neurological signs/symptoms, heartburn, halitosis, nausea, vomiting, bleeding) and conditions (AIDS, neurological disorders, diabetes, scleroderma, or Sjögren's disease)³

Physical Examination

- Watch the patient drink a cup of water (may help distinguish transfer from esophageal dysphagia) and rule out associated neurological findings; otherwise, examination is usually normal

Diagnostic Studies and Laboratory Values

- Laboratory evaluations are usually normal
- Other studies
 - Studies for dysphagia include video fluoroscopy, barium swallow, endoscopy, esophageal manometry, and nasopharyngeal laryngoscopy
 - Transfer dysphagia: video fluoroscopy evaluates swallowing mechanism/pathology²
 - Esophageal dysphagia^{1,4}: endoscopy is usually the first diagnostic procedure of choice
 - Barium swallow may be helpful to define anatomic changes and to rule out oropharyngeal or upper esophageal pathology that may pose a hazard to endoscopic evaluation (e.g., Zenker's diverticulum)
 - Esophageal manometry can be performed to evaluate motility disorders

Guide to Acute Management

- Early consultation of the appropriate services (consider Neurology, Speech pathology, and Radiology)
- Consider consulting Gastroenterology for acute dysphagia, because gastroenterology could be secondary to food impaction and is considered an emergent indication for endoscopy, or when initial workup fails to reveal a diagnosis and endoscopy is indicated as the next step in management

Odynophagia

Definition, Etiology, and Epidemiology

- Painful substernal sensation associated with swallowing that should not be confused with dysphagia
- Usually indicates ulceration of the esophageal mucosa due to infections (candidiasis, monilia,

herpes simplex virus (HSV), and cytomegalovirus [CMV]),⁵ ingestion of corrosive agents or pills (classically: tetracycline, vitamin C, iron, quinidine, estrogen, aspirin, alendronate, or nonsteroidal anti-inflammatory drugs),⁶ or cancer

Pearls of the History and Physical Examination

History

- Predisposing factors for immunocompromise (diabetes mellitus, HIV/AIDS, immunosuppressive medications, etc.)⁶
- Previous history of esophageal infections, skin lesions, fevers, chills, nausea, vomiting, or bleeding
- Severity of disease should be assessed (i.e., ability to tolerate oral intake)

Physical Examination

- Examination should include inspection of the oral cavity, looking specifically for oral-labial lesions (although 75% of patients with candidal esophagitis have coincident oral infection, the absence of thrush does not exclude the diagnosis and a high degree of suspicion should be maintained)⁷; additionally, examination of the head and neck should be performed, with attention to lymphadenopathy and skin lesions

Diagnostic Studies and Laboratory Values

Blood Tests

- Complete blood count, CMV pp65 in severely immunocompromised patients (level >50 associated with disease)⁸⁻¹⁰; HSV titers (> fourfold increase in titers of IgM can be suggestive of HSV disease but is not sensitive or specific enough to be considered superior to biopsy and culture of tissue)

Other Studies

- Endoscopy should be performed early in most patients except in those with AIDS, in whom an empiric trial of therapy for candidiasis may be considered

Guide to Acute Management

- Neutropenic patients and those unable to tolerate oral intake should be considered for in-patient treatment due to risk of disseminated disease⁶
- For patients with AIDS, empiric treatment with fluconazole 100-200 mg/d for 10-14 days is warranted, given the high prevalence of candidal esophagitis in patients presenting with odynophagia
 - Nystatin swish and swallow 500,000 units 5 times a day for 7-14 days can also be added for topical therapy; if symptoms do not improve in 5-7 days, upper endoscopy should be performed for diagnostic evaluation¹¹
- For neutropenic patients with fungal esophagitis, give intravenous amphotericin B (because of the high risk of fungal dissemination)^{11,12}
- For HSV esophagitis in severely symptomatic immunocompromised patients, treat with acyclovir at 5 mg/kg intravenously every 8 hours for 7-14 days
- For CMV esophagitis, treat with ganciclovir at 5 mg/kg intravenously every 12 hours for 2 weeks; patients who fail this should be considered for foscarnet 90 mg/kg intravenously every 12 hours for 3-4 weeks⁸
- For in-patients, consider infectious disease consultation early in management; consider Gastroenterology consultation for patients who fail to improve with empiric therapy or critically ill patients or those with severe disease

- Prophylaxis with fluconazole 150 mg/week orally can be recommended for patients with HIV



Patient Care Warnings

- Ganciclovir can cause neutropenia
- Foscarnet can cause renal toxicity

References

- ③ 1. Lind CD. Dysphagia: Evaluation and treatment. *Gastroenterol Clin North Am* 2003;32:553-75.
- ① 2. Fiorentino E, et al. Digital cineradiology in the diagnosis and surgical treatment of pharyngo-oesophageal junction motor disorders. *Chir Ital* 2004;56:495-500.
- ③ 3. Mujica VR, Conklin J. When it's hard to swallow. What to look for in patients with dysphagia. *Postgrad Med J* 1999;105:131-34, 141-42, 145.
- ③ 4. Barlow TJ, Bergus GR, Lu CC. Diagnostic imaging in the evaluation of dysphagia. *Am Fam Physician* 1996;53:535-46.
- ③ 5. Mulhall BP, Wong RK. Infectious esophagitis. *Curr Treat Options Gastroenterol* 2003;6:55-70.
- ③ 6. Baehr PH, McDonald GB. Esophageal infections: Risk factors, presentation, diagnosis, and treatment. *Gastroenterology* 1994;106:509-32.
- ③ 7. Wilcox CM. Esophageal disease in the acquired immunodeficiency syndrome: Etiology, diagnosis, and management." *Am J Med* 1992;92:412-21.
- ③ 8. Draskovic N, Jovanovic D, Kuljic-Kapulica N. Early diagnosis of cytomegalovirus infections in organ recipients. *Med Pregl* 2004;57:133-39.
- ③ 9. Pancholi P, Wu F, Della-Latta P. Rapid detection of cytomegalovirus infection in transplant patients. *Expert Rev Mol Diagn* 2004;4:231-42.
- ② 10. Skiest DJ, Crosby C. CMV pp65 antigen testing is of limited utility in the diagnosis of concomitant CMV disease in HIV-infected patients in the HAART era. *J Clin Virol* 2003;28:203-13.
- ③ 11. Mathieson R, Dutta SK. Candida esophagitis. *Dig Dis Sci* 1983;28:365-70.
- ③ 12. Belitsos PC. Management of HIV-associated esophageal disease. *AIDS Clin Care* 1995;7:19-22.

HEPATORENAL AND HEPATOPULMONARY SYNDROMES

Hepatorenal Syndrome (HRS)

Definition, Etiology, and Epidemiology

- Functional renal failure that develops in patients with cirrhosis, acute liver failure, or portal hypertension without identifiable renal pathology (present in 10% of hospitalized patients with cirrhosis and ascites)
- The pathophysiological hallmark of HRS is a severe vasoconstriction of the renal circulation; this vasoconstriction is a compensatory mechanism for the changes caused by splanchnic vasodilation (peripheral arterial vasodilation hypothesis),¹ leading to oliguria
- A precipitating factor can be found in about 50% of cases; the most common are systemic bacterial infections (particularly spontaneous bacterial peritonitis), gastrointestinal bleeding, and large-volume paracentesis without albumin expansion²

Classification

- Type 1: 50% lowering of the creatinine clearance to below 20 mL/min in less than 2 weeks or a doubling of serum creatinine greater than 2.5 mg/dL
- Type 2: less severe renal insufficiency; the main characteristic of type 2 HRS is diuretic refractory ascites

Diagnostic Studies and Laboratory Values

- Diagnosis of exclusion in the setting of acute renal failure in patients with liver disease that depends mainly on the level of serum creatinine
- Diagnostic criteria: only major criteria are diagnostic³
 - Major criteria
 - Serum creatinine >1.5 mg/dL or 24-hour creatinine clearance of <40 mL/min
 - Exclusion of shock, bacterial infections, volume depletion, and use of nephrotoxic drugs
 - No improvement of renal function despite stopping diuretics and volume repletion with 1.5 L of saline
 - Absence of proteinuria, obstructive uropathy, or parenchymal renal disease
 - Minor criteria: urine volume <500 mL/d, urine sodium <10 mEq/L, serum sodium <130 mEq/L, urine osmolarity $>$ plasma osmolarity, and urine red blood cells <50 per high-power field

Guide to Acute Management

General Measures

- Monitor vital signs, fluid intake, daily weights, urine output, and blood chemistries; look for precipitating factors (infection, bleeding)
- Fluid challenge with 1.5 L of normal saline to rule out intravascular volume depletion
- 2 g Na diet for all patients; fluid restriction to 1 L/d for those with serum Na <130 mEq/L
- Stop diuretics, nonsteroidal anti-inflammatory drugs, or angiotensin-converting enzyme inhibitors.
- In the presence of tense ascites, a therapeutic paracentesis of no more than 5 L is recommended (give albumin 8-10 g/L tapped)
- Assess patient candidacy for liver transplantation as soon as possible; liver consultation

- Patients with type 2 HRS can be managed on an outpatient basis with large volume paracentesis with albumin expansion

Therapy: HRS Can be Reversible

- Pharmacological therapy: primary goal is to reverse renal failure from HRS so that liver transplant candidates can undergo transplantation with lower morbidity rate and have survival similar to patients without HRS
- Vasoconstrictors: vasopressin analogues (ornipressin and terlipressin), somatostatin analogues (octreotide), and alpha-adrenergic agonists (midodrine and noradrenaline); these are given in combination with albumin for 1-2 weeks; these medications have to be avoided in patients with cardiac disease, peripheral vascular disease, and/or cerebrovascular disease
 - Terlipressin (start with 0.5 mg IV every 4 hours) and albumin (1 g/kg on first day followed by 20-50 g/d) is associated with significant improvement in glomerular filtration rate and reduction of serum creatinine below 1.5 in 60%-75% of patients^{4,5}
 - Midodrine (start with 2.5-7.5 mg PO TID) and octreotide (start with 100 µg SC TID) + albumin (as above) is also associated with good response^{6,7}
- Transjugular intrahepatic portosystemic shunt (TIPS): not recommended in patients with Child-Pugh score >12; TIPS does not normalize renal function to the same extent as vasoconstrictors; better outcomes for patients with type 2 HRS⁸
- Dialysis: hemodialysis and peritoneal dialysis are not routinely recommended in HRS; they are considered reasonable options for suitable liver transplant candidates as a bridge for transplantation when there is no response to vasoconstrictors or TIPS
- Liver transplantation is the only curative treatment

Patient Care Warnings

- Urine sodium <10 mEq/L does not make the diagnosis of HRS
- Pharmacological therapy and TIPS can reverse HRS but must be considered a bridge for liver transplantation

Hepatopulmonary Syndrome (HPS)

Definition, Etiology, and Epidemiology

- Disorder of pulmonary oxygenation, occurring in the setting of liver disease or portal hypertension
- Found in 4%-20% of patients with liver cirrhosis⁹
- The pathophysiological hallmark of HPS is microvascular dilation of the pulmonary arterial circulation; this impairs ventilation perfusion matching, resulting in anatomical and functional shunt physiology, leading to hypoxemia

Pearls of the History and Physical Examination

- History: most common symptom is progressive dyspnea that occurs predominantly on exertion
- Physical examination: platypnea (shortness of breath exacerbated by sitting up, improved by lying supine) and orthodeoxia (hypoxemia exacerbated by upright position) are less sensitive but more specific findings

Diagnostic Studies and Laboratory Values

- Blood tests: pulse oximetry and/or room air blood gases with patient sitting up are the first screening tests
 - O_2 saturation $<97\%$ and $PO_2 < 80$ mm Hg with a high A-a gradient (>20 mm Hg) warrant further investigation
- Pulmonary function tests rule out other causes of hypoxemia
- Radiology
- Contrast echocardiography is the preferred screening test for intrapulmonary vasodilation; positive test result shows evidence of intrapulmonary shunting (delayed contrast appearance in the left heart)¹⁰
 - If a patient with liver disease or portal hypertension has a positive contrast echocardiography result, in the absence of significant cardiopulmonary disease, a diagnosis of HPS is made¹¹
- Technetium-labeled (microaggregate albumin) scan, pulmonary angiography, and cardiac catheterization can be considered for situations where diagnostic uncertainty persists after initial evaluation

Guide to Acute Management

- The first step is the correction of hypoxemia by oxygen administration
- Pharmacological therapy is still experimental
- Liver transplantation is the only successful, long-term treatment currently available for HPS
- About 85% of patients experience improvement of symptoms or resolution of hypoxemia, but this can take more than 1 year¹²
- Mortality rate after liver transplantation is significantly increased in patients with HPS¹³



Patient Care Warnings

- HPS has to be considered in patients with liver disease or portal hypertension presenting with dyspnea and/or hypoxemia
- Contrast echocardiography is the preferred screening test for HPS
- Liver transplantation is the only curative treatment available

References

- ③ 1. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8: 1151-57.
- ② 2. Gines A, Escorsell A, Gines P. Incidence, predictive factors and prognosis of hepatorenal syndrome in cirrhosis. *Gastroenterology* 1993;105:229-36.
- ③ 3. Arroyo V, Gines P, Gerbes A, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996;23:164-76.
- ② 4. Uriz J, Gines P, Cardenas A. Terlipressin plus albumin infusion: An effective and safe therapy of hepatorenal syndrome. *J Hepatol* 2000;33:43-48.
- ② 5. Moreau R, Durand F, Poynard T. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study. *Gastroenterology* 2002;122:923-30.
- ① 6. Angeli P, Volvin R, Gerunda P. Reversal of type 1 hepatorenal syndrome with the administration of midodrine and octreotide. *Hepatology* 1999;29:1690-97.
- ② 7. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2004;40:55-64.
- ③ 8. Boyer TD. Transjugular intrahepatic portosystemic shunt. Current status. *Hepatology* 2003;124:1700-10.
- ① 9. Schenk P, Schoniger-Hekele M, et al. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology* 2003;125:1042-52.
- ① 10. Abrams GA, Jaffe CC, et al. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. *Gastroenterology* 1995;109: 1283-88.

- ③ 11. Gaines DI, Fallon MB. Hepatopulmonary syndrome. *Liver Int* 2004;24:397-401.
- ② 12. Philit F, et al. Late resolution of hepatopulmonary syndrome after liver transplantation. *Respiration* 1997;64:173-75.
- ② 13. Arguedas M, et al. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology* 2003; 37:192-97.

ACUTE AND CHRONIC DIARRHEA

Definitions, Etiology, and Epidemiology¹⁻⁴

- Acute diarrhea (AD): diarrhea <4 weeks' duration, most lasting < 4 days
- Chronic diarrhea (CD): diarrhea >4 weeks' duration
- Three or more bowel movements (BMs) per day is abnormal, and 200 g/d is upper limit of stool weight
- More than 450,000 hospitalizations each year are due to gastroenteritis, comprising 1.5% of all adult hospitalizations annually
- Differential diagnosis of acute diarrhea⁴: infectious (bacterial, viral, parasitic), food poisoning, medications

Pearls of the History and Physical Examination^{2,4,5}

History

- Duration, frequency, symptoms of dehydration or volume depletion (suggest a higher stool output), acute weight loss (correlates with higher stool output if rehydration is suboptimal)
- Stool characteristics: blood (malignancy or IBD), food particles (malabsorption, maldigestion, or rapid intestinal transit), water (osmotic or secretory process), mucus (IBS), pus (infection or inflammation)
- Relationship of BM to meals or fasting, day versus night (nighttime diarrhea waking patient from sleep)

DIFFERENTIAL DIAGNOSIS OF CHRONIC DIARRHEA⁴

Chronic watery diarrhea

- Osmotic diarrhea: osmotic laxatives (e.g., Mg^{2+} , PO_4^{3-} , SO_4^{2-}), carbohydrate malabsorption
- Secretory diarrhea: congenital syndromes (e.g., congenital chloridorrhea), bacterial toxins, ileal bile acid malabsorption, inflammatory bowel disease (IBD) (ulcerative colitis [UC], Crohn's disease, microscopic colitis [lymphocytic colitis, collagenous colitis], diverticulitis)
- Vasculitis
- Drugs and poisons
- Laxative abuse (stimulant laxatives)
- Disordered motility/regulation: postvagotomy diarrhea, postsympathectomy diarrhea, diabetic autonomic neuropathy, irritable bowel syndrome
- Endocrine diarrhea: hyperthyroidism, Addison's disease, gastrinoma, vasoactive intestinal peptide-producing tumor, somatostatinoma, carcinoid syndrome, medullary carcinoma of the thyroid, mastocytosis
- Other tumors: colorectal cancer, villous adenoma, lymphoma
- Idiopathic secretory diarrhea: epidemic secretory (Brainerd's) diarrhea, sporadic idiopathic secretory diarrhea

Chronic inflammatory diarrhea

- IBD: UC, Crohn's disease, diverticulitis, ulcerative jejunoileitis
- Infectious diseases: pseudomembranous colitis, invasive bacterial infections (e.g., tuberculosis, *Yersinia*), ulcerating viral infections (e.g., cytomegalovirus, herpes simplex), invasive parasitic infections (e.g., amebiasis, strongyloidiasis)
- Ischemic colitis
- Radiation colitis
- Neoplasia: colorectal cancer, lymphoma

Chronic fatty diarrhea

- Malabsorption syndromes: mucosal diseases (e.g., celiac disease, Whipple's disease), short bowel syndrome/postresection diarrhea, small bowel bacterial overgrowth, mesenteric ischemia
- Maldigestion: pancreatic exocrine insufficiency, inadequate luminal bile acid concentration

Prevalence of chronic diarrhea = 5%

suggests organic cause), fecal urgency or incontinence (suggests muscular disorder or impaired rectal compliance)

- Associated symptoms: abdominal pain, flatulence, bloating, cramps, fever, weight changes
- Differentiate IBS from other functional and organic causes; characterized by the presence of abdominal pain associated with defecation, variable stool consistency, periods of constipation, long history of diarrhea (beginning at young age), passage of mucus, exacerbation of symptoms by stress
- Other medical problems/past medical and surgical history: medications, diet, recent travel, rural versus urban dwelling, source of drinking water, occupation, sexual orientation, illicit drug or alcohol use, laxative abuse (fixation on body image, weight)

Physical Examination

- General appearance (toxic versus nontoxic); assess for volume status and hyperthyroidism
- Abdominal examination: status of bowel sounds, distention, tenderness, hepatosplenomegaly
- Musculoskeletal examination (IBD with associated arthritis)
- Vascular examination (abnormal result could suggest peripheral vascular disease involving the mesenteric supply)
- Lymphadenopathy (suggesting presence of AIDS or lymphoma)
- Skin changes (e.g., Addison's disease)

Diagnostic Studies and Laboratory Values^{1,2,4,6-9}

Acute Diarrhea

- Blood tests: complete blood count (anemia), Chem-7 (electrolyte disturbances), serological testing for amebiasis (if suspected)

- Stool studies: stool white blood cells (WBCs) (stool cultures unlikely to grow pathogens in absence of fecal WBCs), stool ova and parasites, ELISA for *Giardia* (if clinical suspicion), stool for *Clostridium difficile* (if antibiotic therapy in preceding 3 months or hospitalized/institutionalized patient)
- Endoscopy
 - Flexible sigmoidoscopy to obtain mucosal biopsy in toxic patients, those with blood in stool, or those with persistent acute diarrhea
 - Colonoscopy in AIDS patients in order to evaluate right colon
- Radiology: abdominal films to evaluate for stool contents, colitis, evidence of ileus, or megacolon

Chronic Diarrhea: Same Evaluation as for Acute Diarrhea

- Stool studies: timed or random stool collection (preferably timed to calculate stool output), measuring stool [Na] and [K]
- $(290 \text{ mOsm/kg} - 2 \times ([\text{Na}] + [\text{K}])) = \text{stool osmotic gap}$
 - A small osmotic gap ($<50 \text{ mOsm/kg}$) suggests excess water is retained in stool 2° incomplete electrolyte absorption as seen with secretory diarrhea
 - A large osmotic gap suggests osmotic diarrhea due to ingestion of some poorly absorbed material
 - Stool osmolality rises once stool is collected due to bacterial fermentation; this value is not useful in calculating stool osmotic gap
 - Low stool pH indicative of carbohydrate malabsorption
 - Fecal occult blood test, WBCs, or surrogate such as fecal lactoferrin can be done to evaluate for ongoing inflammatory diarrhea or malignancy
 - Stool fat (quantitative or qualitative)
 - $>10\%$ stool fat content suggests pancreatic exocrine insufficiency

- Steatorrhea (as assessed by qualitative Sudan stain) suggests malabsorption in small intestine
- Laxative screen if suspicious for laxative abuse

PEARLS FOR DIAGNOSING TYPES OF DIARRHEA

Secretory Diarrhea	Osmotic Diarrhea	Inflammatory Diarrhea	Fatty Diarrhea
Impaired salt and water absorption <i>Aeromonas</i> and <i>Pleisiomonas</i> can cause secretory diarrhea and require special cultures Special laboratory studies needed to find coccidia and microsporidia in the stool Small bowel biopsy to look for other pathogens or culture of small bowel aspirate to assess for bacterial overgrowth SBFT, endoscopy with biopsy, CT abdomen to look for structural abnormalities (short bowel, fistula, mucosal diseases, IBD, tumors)	Magnesium (Mg) ingestion • Excretion of >15 mmol or 30 mEq Mg daily in stool or [Mg] in stool water >45 mmol/L or 90 mEq/L is suggestive • Intentional (laxative abuse) • Inadvertent (antacids, mineral supplements) Carbohydrate malabsorption • Seen with lactose ingestion in lactase deficiency, sorbitol/mannitol ingestion, fructose, or use of acarbose in diabetics • Leads to excess carbohydrate delivery to the colon	Look for stool WBCs or blood in stool Evaluate for structural problems with SBFT, CT scan, endoscopy (upper and/or lower) with biopsy as appropriate Most common infectious causes are <i>C. difficile</i>, CMV, amebiasis, and TB	Steatorrhea is due to impaired fat solubilization, digestion, or absorption • 7 g of fat in stool, >9% fat intake in 24 hours However, steatorrhea can be seen in diarrhea from other causes Fecal fat excretion of 7-14 g/24 hours has low specificity for impaired fat absorption in patients with diarrhea Fecal fat excretion of >14 g/24 hours is suggestive of impaired fat absorption in patients with diarrhea

PEARLS FOR DIAGNOSING TYPES OF DIARRHEA *(Continued)*

Secretory Diarrhea	Osmotic Diarrhea	Inflammatory Diarrhea	Fatty Diarrhea
Serum-peptide levels are best done for patients who have imaging or symptoms consistent with tumor syndromes (e.g., chronic diarrhea and flushing with carcinoid syndrome) No utility in testing for bile-acid malabsorption: most effective to try course of bile-acid sequestrants; if clinical improvement, this is diagnostic and therapeutic	• These are fermented to short-chain fatty acids, hydrogen, and carbon dioxide • Results in low stool water pH and gas/bloating Should resolve when causative agent is no longer ingested, except in patients with carbohydrate or Mg malabsorption due to some other mechanism like short bowel syndrome		Above ranges need to be adjusted in patients with diarrhea, given decreased dietary fat often seen in these patients Sudan stain or fecal smear can provide qualitative estimation using semiquantitative methods to measure number and size of fat globules Good correlation between quantitative and qualitative techniques Mucosal diseases causing steatorrhea have dilute stool fat concentration due to unabsorbed water ^{2°} impaired water/electrolyte absorption Fecal fat concentration >9.5 g fat in 100-g stool is usually seen with pancreatic or biliary steatorrhea SBFT, CT scan, small bowel biopsy, and aspirate useful in evaluation Pancreatic enzyme supplementation can be diagnostic and therapeutic

SBFT: small bowel follow-through; CT: computed tomography; CMV: cytomegalovirus; TB: tuberculosis

Guide to Acute Management^{1,4}

- Fluid and electrolyte repletion with oral and IV agents
- Empiric antibiotics in patients with high pretest probability of acute infectious etiology (e.g., high prevalence of a particular pathogen in a population, sick contacts, recent travel)
- Empiric antibiotics in toxic patients with concern for acute infectious etiology
- Antidiarrheals (loperamide, diphenoxylate with atropine)
- No definitive data suggesting that the use of these agents impairs clearance of offending pathogens in acute infectious diarrhea
- In chronic diarrhea, empiric course of metronidazole or a fluoroquinolone before extensive testing is not unreasonable
- Use of bile-acid sequestrants or pancreatic enzyme replacement can be diagnostic and therapeutic for patients with steatorrhea



Patient Care Warnings

- Initial inpatient management is aggressive fluid and electrolyte repletion
- Thorough history and physical examination are integral to proper diagnosis and management
- Use good clinical judgment in ordering appropriate diagnostic tests as early as possible during hospital course to expedite workup and management
- Early empiric antibiotics when indicated should not replace diagnostic testing

- For patients with chronic diarrhea with no effective therapy, opiates can be used to manage symptoms (start low dose and titrate slowly as needed)
- Stool-bulking agents such as psyllium or fiber-containing agents can change stool consistency

References

- ③ 1. Dupont HL. Guidelines on acute infectious diarrhea in adults. *Am J Gastroenterol* 1997;92:1962.
- ③ 2. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464.
- ③ 3. Talley NJ, Weaver AL, Zinsmeister AR, et al. Self reported diarrhea: What does it mean? *Am J Gastroenterol* 1994;89:1160.
- ③ 4. Schiller LR. Diarrhea. *Med Clin North Am* 2000;84:259
- ③ 5. Thompson WG, Longstreth GF, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45(Suppl 2):43.
- ② 6. Siletti RP, Lee G, Ailey E. Role of stool screening tests in diagnosis of inflammatory bacterial enteritis and in selection of specimens likely to yield invasive enteric pathogens. *J Clin Microbiol* 1996;34:1161.
- ③ 7. Brar HS, Surawicz CM. Pseudomembranous colitis: An update. *Can J Gastroenterol* 2000;14:51.
- ② 8. Fine KD, Fordtran JS. The effect of diarrhea on fecal fat excretion. *Gastroenterology* 1992;102:1936.
- ③ 9. Simko V. Fecal fat microscopy: Acceptable predictive value in screening for steatorrhea. *Am J Gastroenterol* 1981;75:204.

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RHEUMATOLOGY

SYSTEMIC LUPUS ERYTHEMATOSUS

Definition, Etiology, and Epidemiology

- Systemic lupus erythematosus (SLE) is an autoimmune disease with a variety of manifestations related to production of autoantibodies to components of the cell nucleus (antinuclear antibodies [ANA])
- Primarily affects women ages 15–40 years; female-to-male predominance 6–10:1; blacks > whites
- Other possible associations include socioeconomic status, familial aggregates, or in association with other autoimmune diseases
- Immune complex deposition/inflammation affects almost every organ system

DIAGNOSTIC CRITERIA

Diagnostic Criteria	Comment and Presenting Symptoms
Malar rash	Erythema over the malar eminences; usually spares nasolabial folds
Discoid lesions	Small, rounded, well circumscribed, usually on face/scalp or other areas of sun exposure, hair loss can occur on scalp
Oral ulcers	Usually painless and most commonly on hard palate
Photosensitivity	Skin rash as a result of sun exposure

(Continued on following page)

DIAGNOSTIC CRITERIA *(Continued)*

Diagnostic Criteria	Comment and Presenting Symptoms
Arthritis	Often manifest as arthralgias; joints may have redness, swelling, or tenderness; most commonly affects knees, hands/fingers, and ankles
Serositis	Pleuritis (pleural pain, pleural rub, or effusion) or pericarditis/pericardial effusion; presents as dyspnea, chest pain, or cough; abdominal pain and ascites with lupus peritonitis
Renal disorder	Proteinuria >0.5 g/d or cellular casts (red, hemoglobin, granular, tubular, or mixed); edema, decreased urine output
Neurological disorder	Cerebritis leading to seizures or psychosis; can also present with altered mental status, weakness, or other neurological complaints
Hematological disorder	Hemolytic anemia, leukopenia ($<4000/\text{mm}^3$), lymphopenia ($<1500/\text{mm}^3$), or thrombocytopenia ($<100,000/\text{mm}^3$) presenting with fatigue, jaundice, or bleeding.
Immunological disorder	Anti-double-stranded DNA antibodies (anti-dsDNA), anti-Smith antibodies (anti-Sm), or positive antiphospholipid antibodies
Antinuclear antibody	Abnormal titer ANA (in the absence of drugs known to cause drug-induced lupus syndrome)

Must have 4 out of 11 criteria to meet American College of Rheumatology criteria^{1,2}

Pearls of the History and Physical Examination^{1,2}

- Symptoms noted in table above
- Constitutional: fever, sore throat, aches, pains, malaise, fatigue, weight loss, anorexia

- Red, painful subcutaneous nodules on lower extremities (erythema nodosum) or pale purple reticular or lacy outline of veins in lower extremities (livedo reticularis)
- Symptoms of infections due to immune suppression from SLE or treatment
- Cushingoid appearance: buffalo hump, moon facies, truncal obesity, striae if previously treated with steroids
- Examine nailbeds for capillaropathy (dilated capillaries at the edge of nailbed, usually seen with magnifier on ophthalmoscope)
- Lymphadenopathy and hepatosplenomegaly can also be observed in SLE
- Pleural and pericardial rubs or blunted breath or heart sounds indicating effusions; note valvular murmurs, “Velcro-type” rales indicating pulmonary fibrosis in those with advanced pulmonary disease
- Manifestations of deep vein thrombosis (DVT) and pulmonary emboli (PE): unilateral leg swelling, loud P_2 , hypoxia

Diagnostic Studies and Laboratory Values

- Routine laboratory tests: complete blood count with differential; routine serum chemistries including blood urea nitrogen/creatinine; liver function tests as indicated by signs/symptoms (may have low albumin due to acute illness)
- Coagulation factors: elevated partial thromboplastin time: consider antiphospholipid antibodies, anticardiolipin antibody, lupus anticoagulant, and β_2 -glycoprotein-1
- 24-hour urine test for proteinuria and creatinine clearance
- Pregnancy test in all women of childbearing age
- With evidence of hemolysis: reticulocyte count,

lactate dehydrogenase, haptoglobin, total bilirubin, direct/indirect antibody test (direct antiglobulin test or Coombs' test)

- Chest x-ray: infiltrates, effusions, cardiac silhouette
- Electrocardiogram (ECG): may show findings consistent with PE (right heart strain, new right bundle branch block, tachycardia, deep S in I, Q in III, and inverted T in III) or may show evidence of ischemia
- Erythrocyte sedimentation rate, C-reactive protein as indicators of inflammation
- Antibodies: ANA (send only once for initial screening), anti-DS DNA (check with each flare as titers increase and decrease with disease activity), C3/C4 (titers decrease with acute disease flare); other antibody tests: anti-SM, anti-SSA(Ro), anti-SSB(La), anti-RNP, anti-histone Ab (with suspicion for drug induced lupus)
- Lower extremity Doppler ultrasound, ventilation/perfusion scanning, or computed tomography scan if suspicion for DVT or PE
- Serial cardiac enzymes and ECGs with history suggestive of acute coronary syndrome³

Guide to Acute Management⁴

- Prompt rheumatology, nephrology, neurology, or pulmonary consultation is warranted for life- or organ-threatening illness

Suspected Diagnosis	Management Guidelines
Cerebritis	Consider lumbar puncture to rule out infection Cerebrospinal fluid may have elevated cell counts/protein but can be completely normal, even in severe cerebritis

Suspected Diagnosis	Management Guidelines
Nephritis: affects 1/2-2/3 of all patients, classified by the World Health Organization (WHO), based on histology and location of deposition of immune complexes	Note amount of proteinuria, presence/absence of serum markers (i.e., low complement activity), serum creatinine Prompt rheumatology and nephrology consultation, especially with newly diagnosed patients, those with increasing proteinuria, and/or with active urinary sediment Renal biopsy to assess WHO classification
Serositis/pleuritis/pericarditis	Echocardiogram with suspicion for pericardial involvement, especially with signs or symptoms of pericardial effusion/cardiac tamponade Pleural effusion: perform thoracentesis and send for analysis, including lactate dehydrogenase, total protein, glucose, cell count, and pH; effusion typically exudative
Pulmonary hemorrhage/diffuse alveolar hemorrhage	Manifestation of acute lupus pneumonitis; suggested by falling hematocrit level and pulmonary infiltrates; mortality rate approaches 50%; supplemental oxygen includes intubation and mechanical ventilation if indicated
Manifestations of antiphospholipid antibodies	Stroke, myocardial infarction, thrombosis including DVT, pulmonary embolus Heparin for anticoagulation if indicated and no contraindications noted

TREATMENT SPECIFICS⁴

Treatment	Dosing	Indication	Side Effects	Special Consideration/Monitoring
NSAIDs/COX-2 inhibitors ⁵	Drug-specific	Pleuritis, pericarditis, headaches, musculoskeletal complaints	Exacerbation of kidney disease gastrointestinal (GI) bleeding	Consider concurrent acid suppression for reduced GI toxicity
Steroids ⁶	(1) 5-30 mg daily prednisone (2) Higher doses of prednisone: 1-2 mg/kg/d (3) Consider 3-day pulse 1000 mg methylprednisolone/day	(1) Arthritis, serositis, skin disease, constitutional symptoms (2) Nephritis, cerebritis, severe hemolytic anemia, vasculitis (3) Life-threatening illness	Weight gain, hyperglycemia, hyperlipidemia, osteoporosis, edema	Consider calcium/vitamin D supplementation; prophylaxis against <i>Pneumocystis carinii</i> with long-term use
Cyclophosphamide (Cytoxan) ⁷⁻⁹	IV bolus regimen 0.5-1 g/mm ² with adequate IV hydration; Mesna at 20% of total cyclophosphamide dose to prevent hemorrhagic cystitis; daily oral dosing also used at 50-100 mg/d	(1) Primarily in WHO class IV diffuse proliferative nephritis (2) WHO class V and in less severe disease that fails corticosteroids alone	Nausea, vomiting, hair loss	Major early toxicities: (1) Myelosuppression with dose-dependent leukopenia, with nadir occurring 8-12 days after IV dosing (2) Hemorrhagic cystitis; late toxicities include myeloproliferative disorders, malignancy, immunosuppression, and secondary infertility

Treatment	Dosing	Indication	Side Effects	Special Consideration/Monitoring
Mycophenylate mofetil (Cellcept) ¹⁰	500-1000 mg po bid	Alternative treatment for lupus nephritis in combination with steroids	Leukopenia, nausea, diarrhea	Steroid-sparing agent; may also be used after cyclophosphamide as maintenance therapy for nephritis
Hydroxychloroquine (Plaquenil) ¹¹	200-600 mg/d either single or divided doses based on body weight	Constitutional and musculoskeletal complaints	Headache, myalgia, rash, GI upset	Eye toxicity: patients need baseline eye examination, including visual acuity, slit lamp, fundoscopic, and visual field testing and every 6-12 months thereafter
Methotrexate ¹²	15-20 mg po/week; may be able to dose at 7.5-15 mg po/week for fewer side effects	Most commonly in rheumatoid arthritis but also used in SLE for non-life-threatening illness	Serum liver test elevations and GI complaints, cirrhosis, pulmonary disease/fibrosis	Check hepatitis serologies in high-risk patients Consider chest x-ray and pulmonary function tests
Azathioprine (Imuran)	1 mg/kg/d	Alternative treatment for lupus nephritis, in combination with steroids	Myelosuppression hepatotoxicity, lymphoproliferative disorders	Associated with a hypersensitivity syndrome presenting with fever, rash, and elevated transaminases



Patient Care Warnings

- Begin high-dose (1 g/d) pulse steroids in patient with life-threatening complications of lupus, such as alveolar hemorrhage
- Consider lupus anticoagulant in young patients presenting with DVT or PE
- Remember calcium supplementation and possible *P. carinii* pneumonia prophylaxis with long-term steroid use

References

- ③ 1. Klippel JH, ed. Primer on the Rheumatic Diseases, 12th ed. Atlanta, Arthritis Foundation Atlanta, 2001.
- ③ 2. Hill JA. Systemic lupus erythematosus. *N Engl J Med* 1994; 330:1871-79.
- ③ 3. Asanuma Y, et al. Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; 349:2407-15.
- ③ 4. Wallace DJ. Management of lupus erythematosus: Recent insights. *Cur Opin Rheum* 2002;14:212-19.
- ③ 5. Ostenson M, Villiger PM. Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus. *Lupus* 2000;9: 566-72.
- ③ 6. Boumpas DT, Chrousos GP, Wilder RL, et al. Glucocorticoid therapy for immune-mediated diseases: Basic and clinical correlates. *Ann Intern Med* 1993;119:1198-1208.
- ① 7. Gourley MF, Austin HA, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis: A randomized, controlled trial. *Ann Intern Med* 1996;125:549-57.
- ③ 8. Ortmann RA, Klippel JH. Update on cyclophosphamide for systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000;26:363-75.
- ③ 9. Contreras G. Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004;350:971-80.
- ① 10. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenylate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Eng J Med* 2000;343:1156-62.
- ③ 11. The Canadian Hydroxychloroquine Study Group. A random-

ized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Eng J Med* 1991;324:150-54.

12. Carniero JR, SatoEI. Double-blind, randomized, placebo controlled trial of methotrexate in systemic lupus erythematosus. *J Rheumatol* 1999;26:1275-79.

LARGE VESSEL VASCULITIS

Definition, Etiology, and Epidemiology

- The vasculitidies that involve the large vessels include two main entities: giant cell arteritis (GCA), which includes temporal arteritis and aortitis, and Takayasu’s arteritis
- A subset of patients with GCA may also suffer from polymyalgia rheumatica (PMR)
- Whereas the vasculitidies that affect the small and medium arteries involve mainly perivascular inflammatory infiltrates, the inflammation in the large vessels is primarily in the arterial wall
- Hallmarks of the diseases include systemic inflammation, vascular inflammation, and vascular insufficiency^{1,2}

	GCA	Aortitis	Polymyalgia Rheumatica	Takayasu’s Arteritis
Affected tissues; hallmarks of disease	Extracranial arteries of the head	Aorta	Pain in shoulders and hips	Aorta and its major branches; can also affect pulmonary and coronary arteries

(Continued on following page)

	GCA	Aortitis	Polymyalgia Rheumatica	Takayasu's Arteritis
Patient population	Age >50 years; increased incidence with age; females > males; European descent ¹	Age >50 years; increased incidence with age; females > males; European descent ¹	Age >50 years; increased incidence with age; females > males; European descent ¹	Adolescent girls and young women; age <40 years but can start later in Asians in whom it is more common
Mechanism of inflammation	Mononuclear cell infiltrate with T lymphocytes and macrophages, which enter the vessel wall via the vasa vasorum; biopsy reveals granulomatous inflammation, multinucleated giant cells ³	Mononuclear cell infiltrate with T lymphocytes and macrophages, which enter the vessel wall via the vasa vasorum; biopsy reveals granulomatous inflammation, multinucleated giant cells ³	Mononuclear cell infiltrate with T lymphocytes and macrophages, which enter the vessel wall via the vasa vasorum; biopsy reveals granulomatous inflammation, multinucleated giant cells ³	

Pearls of the History and Physical Examination²

- Each form of vasculitis has specific symptoms/location (as noted in the following table); each of these entities may manifest with systemic symptoms, including fever, night sweats, weight loss, anorexia, and depression

	GCA	Aortitis	Polymyalgia Rheumatica	Takayasu's Arteritis
Symptoms	Headaches, scalp tenderness, jaw claudication (pain with prolonged talking or chewing) Acute ischemic optic neuropathy: sudden painless loss of vision, which may be preceded by transient vision loss during activity or straining	Arm claudication Raynaud's phenomenon Symptoms of aortic aneurysm or aortic insufficiency May often lack symptoms of temporal arteritis ³	Pain and stiffness in the shoulder and pelvic girdle muscles Can overlap with temporal arteritis or aortitis	Depends on vascular bed involvement: Common carotid: visual effects, strokes, transient ischemic attack, syncope Vertebral: dizziness and visual impairment Subclavian: arm claudication and pulselessness Aortic arch: aortic insufficiency; heart failure Pulmonary: dyspnea, chest pain Coronary: angina Superior mesenteric: abdominal angina Renal: hypertension Abdominal aorta: claudication, hypertension, abdominal angina Iliac: claudication
Examination findings	Involved vessels prominent and tender Pulses decreased or absent; vision loss with optic disc edema, optic atrophy, and/or optic disc cuffing on examination 1/3 patients will have normal examination results	Signs of vascular insufficiency Bruits over arteries Discrepant blood pressure readings in upper extremities	Weight loss Myalgias Edema of the hands and/or feet	

Diagnostic Studies and Laboratory Values

Giant Cell Arteritis

- Elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein; temporal artery biopsy remains gold standard; patients may also have hypochromic or normochromic anemia, thrombocytosis, elevated liver function tests, especially alkaline phosphatase
- Even if the ESR is normal, patients still need a biopsy (25% of patients with positive biopsy result for temporal arteritis have normal ESR)
- If the biopsy result is negative on one side with a high clinical suspicion, then biopsy should be performed on the contralateral side as areas of inflammation may be patchy or be separated by normal tissue^{2,3}

Aortitis

- Angiography is the gold standard, although imaging with computed tomography (CT) or magnetic resonance imaging (MRI) can show changes in the vessel wall or narrowing; ultrasound may be less diagnostic unless the luminal stenosis is marked, although some studies have showed efficacy in using this imaging modality

Polymyalgia Rheumatica

- No specific testing; careful consideration of other etiologies of pain, including but not limited to thyroid disorders, cancer, paraneoplastic syndromes

Takayasu's Arteritis

- Angiography, CT, MRI: important to follow the aortic root size for increasing dilation as an indication for surgical repair

Imaging Pearls

- Ultrasound can show concentric wall-thickening, stenosis, and sometimes acute occlusions in temporal artery vessels
- Ultrasound of large vessels in GCA or Takayasu's arteritis may show wall-thickening of the distal subclavian, axillary, and proximal brachial arteries
- Positron emission tomography scanning is also a useful tool to reveal evidence of vasculitis in vessels with diameters larger than 4 mm⁴

Guide to Acute Management

	GCA	Aortitis	Polymyalgia Rheumatica	Takayasu's Arteritis
Treatment	Corticosteroids: do not decrease intimal hyperplasia, but do decrease edema and subsequently decrease ischemia ⁵	Corticosteroids as in GCA Studies with steroid-sparing agents such as methotrexate ⁶ not promising to date	Corticosteroids	Steroids Angioplasty Surgical revascularization
Dose	40-60 mg prednisone daily as initial dose		20 mg prednisone po daily Taper dose by 25 mg every 10-15 days to avoid relapse ⁷	40-60 mg prednisone daily; taper in 2-week intervals by 5 mg daily each time dose decreased Low-dose aspirin and other antiplatelet agents Methotrexate 25 mg po daily ^{8,9}



Patient Care Warnings

- If suspicion is high for GCA based on clinical history and lab tests, do not wait for biopsy results; treat empirically with steroids while biopsy is performed and reviewed as patient may develop blindness rapidly

References

1. Weyand CM. The Dunlop-Dottridge Lecture: The pathogenesis of giant cell arteritis. *J Rheumatol* 2000;27:517-22.
2. Weyand CM. Giant cell arteritis and polymyalgia rheumatica. *Ann Intern Med* 2003;139:505-15.
3. Brack A, Martinez-Taboada V, Stanson A, et al. Disease pattern in cranial and large vessel giant-cell arteritis. *Arthritis Rheum* 1999;42:311-17.
4. Schmidt WA, et al. Use of ultrasound and positron emission tomography in the diagnosis of large vessel vasculitis. *Curr Opin Rheumatol* 2005;17:9-15.
5. Weyand CM, Fulbright JW, Hunder GG, et al. Treatment of giant cell arteritis: Interleukin 6 as a marker of disease activity. *Arthritis Rheum* 2000;43:1041-48.
6. Hoffman GS, Cid M, Hellman D, et al. A multicenter, placebo-controlled study of methotrexate in giant cell arteritis. *Arthritis Rheum* 2000;43:S115.
7. Weyand CM, Fulbright JW, Evans JM, et al. Corticosteroid requirements in polymyalgia rheumatica. *Arch Intern Med* 1999;159:577-84.
8. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu's arteritis. *Ann Intern Med* 1994;919-29.
9. Langford CA, Sneller MC, Hoffman GS. Methotrexate use in systemic vasculitis. *Rheumatol Dis Clin North Am* 1997;23:841-53.

SMALL VESSEL VASCULITIS

Definition, Etiology, and Epidemiology¹

- Vasculitis: inflammation of blood vessel walls
- Inflammatory process affecting vessels smaller than arteries, such as arterioles, venules, and capillaries

- Incidence: 40 cases per million
- The Chapel Hill Consensus Conference on the nomenclature of vasculitis has proposed the following definitions for the different entities:
 - Wegener's granulomatosis (WG): granulomatous inflammation involving the respiratory tract; necrotizing vasculitis affecting small-to-medium vessels
 - Churg-Strauss syndrome (CSS): eosinophil-rich and granulomatous inflammation involving the respiratory tract; necrotizing vasculitis affecting small-to-medium vessels with asthma and peripheral eosinophilia
 - Microscopic polyangiitis (MPA): necrotizing vasculitis with few or no immune deposits affecting the small vessels
 - Henoch-Schönlein purpura (HSP): vasculitis with IgA-dominant immune deposits affecting small vessels
 - Essential cryoglobulinemic vasculitis: vasculitis with cryoglobulin-immune deposits affecting small vessels
 - Cutaneous leukocytoclastic vasculitis: isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis

Pearls of the History and Physical Examination

- Signs and symptoms of systemic vasculitis: patients typically report a flulike syndrome with fever, myalgias, arthralgias, malaise, and weight loss

***Wegener's Granulomatosis*^{1,2}**

- Characterized by upper and lower respiratory symptoms, including sinusitis, purulent drainage, nasal mucosal ulceration, epistaxis, otitis media, saddle-nose deformity, cough, and hemoptysis
- Glomerulonephritis often with microscopic hematuria
- Other findings: peripheral neuropathy, cutaneous manifestations (ulcers, palpable purpura, nodules,

papules, and vesicles), arthritis, ocular manifestations (keratitis, conjunctivitis, scleritis, episcleritis, uveitis, retro-orbital pseudotumor, proptosis)

Churg-Strauss Syndrome

- Syndrome with three phases: allergic rhinitis and asthma, eosinophilic infiltrative disease, and small-vessel vasculitis with granulomatous inflammation
- Peripheral neuropathy in the form of mononeuritis multiplex

Microscopic Polyangiitis

- Most common cause of pulmonary renal syndrome
- 90% of patients have glomerulonephritis
- Same spectrum of manifestations as Wegener's granulomatosis but without the granulomatous inflammation

Cryoglobulinemic Vasculitis³

- Average age of affected patients is 50 years¹
- Frequently associated with infectious causes, including: hepatitis C, B, and A; HIV, Epstein-Barr virus, cytomegalovirus, connective tissue diseases, and myeloproliferative disorders
- Common symptoms (>70%): purpura, arthralgias/arthritis, and weakness
- Frequent symptoms (40%-70%): polyneuropathy (subacute course, predominantly distal, symmetric or asymmetric, motor and/or sensory polyneuropathy, acute mononeuritis multiplex), subclinical lymphocytic alveolitis
- Less common symptoms (<40%): Meltzer's triad (purpura, arthralgias, weakness), renal involvement (nephrotic or nephritic syndrome), secondary Sjögren's syndrome, secondary Raynaud's phenomenon, central nervous system involvement (cerebrovascular accident, diffuse encephalopathy, cerebral vasculitis, cranial neuropathy, hearing loss),

gastrointestinal involvement (abdominal pain, hematochezia, diarrhea, hematemesis, intestinal infarction), cardiac involvement (coronaritis, myocarditis), pulmonary renal syndrome, retinal involvement, secondary arteritis temporalis, myalgia/myositis

***Henoch-Schönlein Purpura*^{1,4}**

- More prevalent during childhood (peak incidence at age 5 years)
- 50% of patients have hematuria
- 20% of patients with evidence of renal failure
- Abdominal pain, mesenteric ischemia, and gastrointestinal bleeding more common in affected adults; potentially lethal

Cutaneous Leukocytoclastic Vasculitis

- Frequently associated with drug exposure: penicillins, aminopenicillins, thiazides, propylthiouracil, allopurinol, sulfa-containing compounds, and retinoids
- Most patients have spontaneous resolution

Diagnostic Studies and Laboratory Values

- No consensus on diagnostic criteria for the various categories of small vessel vasculitis
- In 1999 American College of Rheumatology published an approach to classifying vasculitides for the clinical trials, and these criteria have been widely used for diagnostic purposes (see above Chapel Hill Consensus Conference)
- A careful history and physical examination are essential to the diagnosis (see following table)
- Laboratory tests are nonspecific but may support a diagnosis in the right clinical scenario; during evaluation of a patient with suspected vasculitis it is recommended to obtain antinuclear antibodies, antineutrophilic cytoplasmic antibodies (ANCA), complement levels, cryoglobulins, fecal occult

blood, antibodies to hepatitis B and C, rheumatoid factor, urinalysis, and chemistries

- Nerve conduction velocities with evidence of neuropathy
- Biopsy of involved tissue, such as skin, nerve, muscle, lung, or kidney
- Pathology may suggest etiology:
 - IgA deposits: Henoch-Schönlein purpura
 - IgM/IgG: cryoglobulins
 - Segmental necrotizing and crescentic glomerulonephritis: Wegener's granulomatosis, microscopic polyangiitis

Feature	HSP	CV	MPA	WG	CSS
Signs and symptoms of small vessel vasculitis*	+	+	+	+	+
IgA-dominant immune deposits	+	—	—	—	—
Cryoglobulins in blood and vessels	—	+	—	—	—
ANCA	—	—	+	+	+
Necrotizing granulomas	—	—	—	+	+
Asthma and eosinophilia	—	—	—	—	+

CV: cryoglobulinemic vasculitis

*Purpura, nephritis, abdominal pain, peripheral neuropathy, myalgias, and arthralgias

Guide to Acute Management

ANCA-Positive (Wegener's Granulomatosis and Microscopic Polyangiitis)

- Induction treatment: cyclophosphamide 2 mg/kg/d po for 6-12 months² (preferred) or cyclophosphamide intravenous (IV) and corticosteroids IV (i.e., methylprednisolone 15 mg/kg/d × 3 days with subsequent taper after remission is achieved (3-6 months)⁵
- Maintenance: methotrexate⁶ (if creatinine <2.0 mg/dL) or azathioprine⁷; Wegener's granulomatosis

without renal involvement may be treated successfully with low doses of methotrexate⁶

- Prophylaxis: *Pneumocystis carinii* pneumonia prophylaxis with Bactrim DS 1 tab 3 × week is sufficient; folic acid 1-2 mg/day is needed to reduce the potential toxicity of methotrexate
- Relapses: close surveillance for asymptomatic renal relapse is needed; treatment determined by the severity of relapse and whether patient is currently on immunosuppressive treatment
 - Mild relapse on immunosuppressive therapy: increased steroids and immunosuppressive agents can be considered
 - Severe relapse or relapse off immunosuppressive therapy: new cycle of induction with extension of therapy to 2 years⁸
- Plasmapheresis useful in patients with WG in three circumstances: (1) anti-GBM antibodies, (2) dialysis-dependent renal failure, and (3) possibly in alveolar hemorrhage, although its role in this condition is not very well established^{9,10}
- Complications from cyclophosphamide: opportunistic infections, hemorrhagic cystitis, ovarian and testicular failure, and cancer.
- Biological modulators: medications that have been used include etanercept, infliximab, and rituximab⁸; no conclusions can be drawn regarding their efficacy at this time

Cryoglobulinemic Vasculitis

- No uniform recommendations about the doses and duration of immunosuppressive therapy or addition of plasmapheresis²
- Cyclophosphamide and steroids are the cornerstone of treatment with more severe disease; additional plasmapheresis or cryofiltration is useful in patients with neurological manifestations or rapidly progressive glomerulonephritis

- When clinical remission is achieved or in chronic HCV-associated cryoglobulinemic vasculitis, the use of interferon- α should be strongly considered

Henoch-Schönlein Purpura¹

- Overall excellent prognosis
- Major long-term morbidity is from progressive renal disease; end-stage renal disease noted in 18% of pediatric patients and 28% in adults
- Treatment is controversial but steroids, cyclosporine, cyclophosphamide, intravenous immunoglobulin, plasmapheresis, and azathioprine have been tried with mixed results in uncontrolled, open label, and retrospective trials¹¹⁻¹³

Leukocytoclastic Vasculitis

- Nonsteroidal anti-inflammatory drugs
- Steroids
- Colchicine
- In urticarial form: dapsone



Patient Care Warnings

- Vasculitis can have a very nonspecific presentation and will require a high index of suspicion for diagnosis
- Readily accessible tissue biopsy (skin, kidney) can be the key for confirming a diagnosis

References

- ③ 1. Jennette JC, Falk RJ. Small-vessel vasculitis. *New Engl J Med* 1997;337:1512-23.
- ③ 2. Calbrese L, Duna G. Vasculitis associated with antineutrophil cytoplasmic antibody. In Harris E, Budd R, Firestein G, et al (eds). *Kelley's Textbook of Rheumatology*, 6th ed. Philadelphia, WB Saunders, 2001:1165-84.

- ③ 3. Lamprecht P, Gause A, Gross WL. Cryoglobulinemic vasculitis. *Arthritis Rheum* 1999;42:2507-16.
- ③ 4. Ballinger S. Henoch-Schönlein purpura. *Curr Opin Rheumatol*. 2003;15:591-94.
- ③ 5. Bacon PA. Therapy of vasculitis. *J Rheumatol* 1994;21:788-90.
- ② 6. Sneller MC, Hoffman GS, et al. An analysis of forty-two with Wegener's granulomatosis patients treated with methotrexate and prednisone. *Arthritis Rheum* 1995;38:608-13.
- ① 7. Jayne D, Rasmussen N. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;349:36-44.
- ③ 8. Langford C, Balow J. New insights into the immunopathogenesis and treatment of small vessel vasculitis of the kidney. *Curr Opin Nephrol Hypertens* 2003;12:267-72.
- ③ 9. Glasscock RJ. Intensive plasma exchange in crescentic glomerulonephritis: Help or no help? *Am J Kidney Dis* 1992;20:270.
- ③ 10. Pusey CD. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int* 1991;40:757.
- ② 11. Wang L. Successful treatment of mesenteric vasculitis caused by Henoch-Schönlein purpura with methylprednisolone pulse therapy. *Clin Rheumatol* 2003;22:140-42.
- ② 12. Tarshish P, Bernstein J, Edelmann M. Henoch-Schönlein purpura nephritis: Course of disease and efficacy of cyclophosphamide. *Pediatr Nephrol* 2004;19:51-56.
- ② 13. Hattori M, Ito K, et al. Plasmapheresis as the sole therapy for rapidly progressive Henoch-Schönlein purpura nephritis in children. *Am J Kidney Dis* 1999;33:427-33.

INFLAMMATORY MYOPATHIES

Definition, Etiology, and Epidemiology¹⁻⁴

- Heterogeneous group of disorders characterized by muscle inflammation and proximal muscle weakness: juvenile dermatomyositis, polymyositis (PM), dermatomyositis (DM), and inclusion body myositis
- Incidence of 0.5-8.4/million with bimodal distribution: first peak at age 10-15 years and again at ages 45-60 years; women are affected twice as often as men, except in inclusion body myositis
- Etiology likely multifactorial: environmental triggers

such as infection, autoantibody responses, or a combination of both

- Often seen concurrently with other autoimmune processes; circulating antibodies can be myositis-associated or myositis-specific
- Association with malignancy as a paraneoplastic phenomenon

Pearls of the History and Physical Examination, Diagnostic Studies, and Laboratory Values

SYMPTOMS, PHYSICAL EXAMINATION, AND LABORATORY DATA¹⁻⁴

Presenting Symptoms	Physical Examination Pearls	Pertinent Laboratory Tests/Studies
Symmetric proximal muscle weakness (difficulty rising from chair, climbing stairs, combing hair) Morning stiffness Fatigue Anorexia	Attention to proximal strength of shoulder and pelvic girdle muscles; neck flexors Serial strength examinations to monitor treatment success	Electromyography Serum markers for muscle damage: creatine kinase (CK), aldolase, aspartate aminotransferase, lactate dehydrogenase CK level can reflect disease activity Muscle biopsy Complete blood count, complete metabolic panel, thyroid-stimulating hormone Swallow study
Dysphagia	Cranial nerve patients may suffer pharyngeal muscle weakness	
Rash (dermatomyositis): • Heliotrope rash Gotttron's papules Shawl sign	• Purple periorbital discoloration Raised purple plaques on extensor surface of hands Macular erythema over upper chest	Biopsy of lesion

SYMPTOMS, PHYSICAL EXAMINATION, AND LABORATORY DATA¹⁻⁴ (Continued)

Presenting Symptoms	Physical Examination Pearls	Pertinent Laboratory Tests/Studies
Cardiac symptoms (rare): atrioventricular conduction defects, tachyarrhythmias, myocarditis, congestive heart failure	Tachycardia, jugular venous distention, S3, edema	Brain natriuretic peptide, electrocardiogram and/or echocardiography, elevation in CK, CKMB, or troponin
Pulmonary: dyspnea on exertion	Fine dry crackles	Chest x-ray, pulmonary function tests

Diagnostic Criteria¹⁻⁴

- Proximal muscle weakness
- Elevated serum enzymes derived from muscle
- Myopathic changes on electromyography (EMG)
- Muscle biopsy consistent with inflammation

Electromyography¹⁻⁴

- EMG may reveal this classic triad:
 - Increased insertional activity, fibrillations, and sharp positive waves
 - Spontaneous, bizarre high-frequency discharges
 - Polyphasic motor-unit potentials of low amplitude and short duration
- Complete triad is seen in only 40%-50% of patients
- 10%-15% of patients may have normal EMG

Muscle Biopsy Findings¹⁻⁴

- Polymyositis (PM)
 - Varying amounts of necrosis and regeneration of muscle fibers
 - Inflammatory cell infiltrate is focal and endomysial
 - CD8+ cytotoxic T cells and macrophages found surrounding and invading the nonnecrotic fibers

- Dermatomyositis (DM)
 - Findings may be similar to those of PM
 - Commonly shows perivascular infiltrate of inflammatory cells
 - Higher percentage of B lymphocytes and CD4+ T-helper lymphocytes
 - Perifascicular atrophy (may be diagnostic of DM)
- Inclusion-body myositis
 - Intracellular vacuoles
 - Intracytoplasmic or intranuclear inclusions
 - Myelin figures or myeloid bodies and membranous whorls also common

ANTIBODY-SPECIFIC SYNDROMES³

Autoantibody	Clinical Features
Antisynthetase: most commonly anti-Jo-1	PM or DM with acute onset, fever, arthritis, Raynaud's disease, interstitial lung disease (ILD)
Anti-SRP	PM with very acute onset, often occurs in the fall, severe weakness, palpitations, ILD
Anti-Mi2	DM with V-sign, shawl disease, and cuticular overgrowth

Guide to Acute Management⁵⁻⁹

- Prednisone 1 mg/kg/d; may be given in divided daily doses; consider intravenous (IV) methylprednisolone for severe disease; others give 80-100 mg prednisone daily for 4 weeks, then taper dose over 10 weeks to dosing every other day
- May consider weekly methotrexate 5-15 mg orally or 15-30 mg IV, or azathioprine 2-3 mg/kg/d (maximum of 150 mg/d) alone or in combination with steroids
- Choices for refractory disease include IV immunoglobulin, cyclosporine, or other immunomodulators
- Consult a specialist before using alternative chemotherapies

- Indications for additional agents: need for steroid-sparing therapy, complications of steroids, inability to lower steroid dose without relapse, ineffectiveness of steroids over 2-3 months, rapidly progressive muscle weakness



Patient Care Warnings

- Consider age-appropriate cancer screening (stool guaiac test, breast and pelvic examination/imaging, further imaging based on risk factors or symptoms) for patients who present with new onset myopathy, especially dermatomyositis, but also polymyositis

References

- ③ 1. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975; 292:344-47.
- ③ 2. Tanimoto K, Nakano K, Kano S, et al. Classification criteria for the idiopathic inflammatory myopathies. *Curr Opin Rheumatol* 1997;9:527-35.
- ③ 3. Dalakas M, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet* 2003;362:971-82.
- ③ 4. Plotz PH, Dalakas M, et al. Current concepts in the idiopathic inflammatory myopathies: Polymyositis, dermatomyositis, and related disorders. *Ann Intern Med* 1989;111:143-57.
- ② 5. Bunch TW, Worthington JW, Combs JJ, et al. Azathioprine and prednisone with polymyositis: A controlled, clinical trial. *Ann Intern Med* 1980;92:365-69.
- ② 6. Bunch TW. Prednisone and azathioprine for polymyositis: Long-term follow-up. *Arthritis Rheum* 1981;24:45-48.
- ③ 7. Metzger AL, Bohan A, Goldberg LS, et al. Polymyositis and dermatomyositis: Combined methotrexate and corticosteroid therapy. *Ann Intern Med* 1974;81:182.
- ① 8. Dalakas MC, Illa I, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993;329:1993-2000.
- ③ 9. Qushmaq KA, Chalmers A, Esdaile JM. Cyclosporin A in the treatment of refractory adult polymyositis/dermatomyositis: Population-based experience in 6 patients and literature review. *J Rheumatol* 2000;27:2855-59.

ARTHRITIS

Definition and Epidemiology

- Musculoskeletal complaints account for 315 million outpatient visits every year
- Primary objective during initial evaluation is to determine presence of serious illness

Acute Monoarthritis**Definition, Etiology, and Epidemiology**

- Acute inflammatory process that affects a single joint over the course of days (usually fewer than 2 weeks)
- Potential medical emergency requiring immediate attention
- Gonococcal disease is the most frequent form of monoarthritis in young, sexually active patients in United States¹; female-to-male ratio 3-4:1
- *Staphylococcus aureus* is the most frequent pathogen in nongonococcal arthritis (60%); other bacteria include: non-group A streptococci, gram-negative streptococci, *Streptococcus pneumoniae*, *Borrelia burgdorferi*
- Etiology

Common Causes	Less Common Causes	Rare Causes
Avascular necrosis	Bone malignancies	Amyloidosis
Crystals: monosodium urate, calcium pyrophosphate dehydrate (pseudogout), apatite, calcium oxalate	Enteropathy-associated arthritis	Behçets's syndrome

Common Causes	Less Common Causes	Rare Causes
Hemarthrosis	Hemoglobinopathies	Familial Mediterranean fever
Infection: bacteria, fungi, mycobacteria, viruses, spirochetes	Juvenile rheumatoid arthritis (RA)	Pigmented villous
Internal derangement	Loose body	Relapsing poly-chondritis
Osteoarthritis (OA)	Psoriatic arthritis	Still's disease
Osteomyelitis	RA	Synovioma
Overuse	Reactive arthritis	Synovial metastasis
Trauma	Sarcoidosis	Vasculitis

Pearls of the History and Physical Examination¹⁻³

- Rapid onset: bacterial infection, crystals
- Indolent onset: fungi, mycobacteria
- Risk factors for infectious arthritis: diabetes mellitus, age >80 years, prosthetic joints, recent articular surgery, skin infections, rheumatoid arthritis
- In young patients assess for gonococcal arthritis: sexual history, sequential monoarthritis, enthesitis (inflammation of the tendon sheath), rash (vesiculopustular eruption on an erythematous base on palms and soles), conjunctivitis, urethritis, and diarrhea
- Involvement of the sternoclavicular joint is often seen in intravenous drug users
- Fever, redness, and warmth are frequently seen in infection and crystal-induced arthritis
- Repeated episodes of arthritis that resolve spontaneously are indicative of crystal-induced arthritis
- Presence of tophi (firm subcutaneous deposits of urate over olecranon process, metatarsophalangeal joints, fingers, toes, and helix) suggests gout; tophi are distinguished from rheumatoid nodules by their asymmetric distribution
- Spontaneous osteonecrosis is more often seen in alcoholics, chronic steroid use, hemoglobinopathies,

diabetes mellitus; patients are usually unable to bear weight; they limp and have restrictive movement of the joint

Diagnostic Studies and Laboratory Values^{1,4,5}

Synovial Fluid

- Perform synovial fluid aspiration in every case where infection is considered
- Tests to order on fluid: cell count with differential, Gram's stain, cultures, and crystal examination
- Arthritis can be divided into inflammatory or noninflammatory based on fluid components

Noninflammatory Fluid: WBC <2000	Inflammatory Fluid: WBC >2000
Trauma: fluid transparent or blood-stained (in true hemarthrosis fluid is xanthochromic), WBC <1000	Infection: opaque, WBC >100,000; PMNs >85%, cultures are positive in 90% of nongonococcal infection and <50% in gonococcal infection
Avascular necrosis	Crystals: translucent, WBC 1-75,000, PMNs >50%, culture/Gram's stain-negative MSU: birefringent needle-shaped crystals CPPD: weakly birefringent rhomboidal or rod-shaped crystals
Baker's cyst OA	

WBC: white blood cell; PMN: polymorphic nuclear cells; MSU: monosodium urate monohydrate; CPPD: calcium pyrophosphate dihydrate

Radiological Studies

- Plain films are useful for ruling out fractures and osteomyelitis; tophi and/or joint erosions with overhanging edges support diagnosis of gout; chondrocalcinosis on x-ray supports the diagnosis of calcium pyrophosphate deposition disease

Other Studies

- Blood and urine cultures
- Swabs of urethra, throat, and cervix to evaluate for gonococcal disease

Guide to Acute Management^{1,6-7}

Infectious Arthritis

- Start intravenous (IV) antibiotics early
- If nongonococcal disease is suspected, initiate appropriate coverage for *S. aureus*
- Gram-negative coverage should be considered in immunocompromised subjects
- IV therapy should be continued for at least 2 weeks in nongonococcal disease, followed by oral antibiotics for 2-4 weeks
- Consider early referral to orthopedic surgery

Crystal-Induced Arthritis

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually first-line treatment; should be avoided in patients with renal dysfunction or with high risk for gastrointestinal bleeding (elderly patients, previous peptic ulcer disease, anticoagulation, or on steroids)
- Steroids should preferably be administered intra-



Patient Care Warnings

- Acute monoarthritis should be considered infectious until proved otherwise
- Until infection has been ruled out, corticosteroids should not be injected into a joint
- Crystal-proven gout or pseudogout does not rule out concomitant infection

articularly; if given orally start 30-50 mg of prednisone per day and taper over 5-10 days

- Oral colchicine is rarely given due to high incidence of side effects

References

1. Siva C, Velazquez C, Mody A, et al. Diagnosing acute monoarthritis in adults: A practical approach for the family physician. *Am Family Physician* 2003;68:83-90.
2. Cibere J. Rheumatology: Acute monoarthritis. *Can Med Assoc J* 2000;162:1577-83.
3. Cush JJ, Lipski P. Approach to articular and musculoskeletal disorders. In *Harrison's Principles of Internal Medicine*, 15th ed. McGraw Hill, 2001:1979-87.
4. Fye KH. Arthrocentesis, synovial fluid analysis, and synovial biopsy. In Klippel JH, Crofford LJ, Stone JH, et al, eds. *Atlanta, Atlanta Arthritis Foundation*; 2001:138-39.
5. Shmerling RH, Delbanco TL, Tosteson AN, et al. Synovial fluid tests. What should be ordered? *JAMA* 1990;264:1009-14.
6. McCune WJ, Golbus J. Monoarticular arthritis. In Kelley WN, Ruddy S, Harris ED Jr, et al, eds. *Textbook of Rheumatology*, 6th ed. Philadelphia, W.B. Saunders, 2001:367-77.
7. Groff GD, Franck WA, Raddatz DA. Systemic steroid therapy for acute gout: A clinical trial and review of the literature. *Semin Arthritis Rheum* 1988;31:803-805.
8. Goldenberg DL. Bacterial arthritis. In Kelley WN, Ruddy S, Harris ED Jr, et al, eds. *Textbook of rheumatology*. 5th ed. Philadelphia, W.B. Saunders, 1997:1435-49.

Acute Oligoarthritis and Polyarthritis

Definition, Etiology, and Epidemiology^{1,2}

- Oligoarthritis defined as involvement of four or fewer joints
- Defined as acute if duration of pain fewer than 6 weeks
- Six clinical factors are helpful in narrowing possible causes^{1,2}: disease chronicity, presence of inflammation, distribution of joints, extra-articular manifestations, disease course, patient demographics

INFLAMMATORY ARTHRITIS		
Peripheral: Oligoarticular	Peripheral: Polyarticular	Peripheral and Axial
Psoriatic arthritis	Rheumatoid arthritis	Ankylosing spondylitis
Reactive arthritis	Systemic lupus erythe- matosus	Reactive arthritis
Rheumatic fever	Viral arthritis (par- vovirus)	Enteropathy- associated arthritis
Gout	Psoriatic arthritis (rare)	Psoriatic arthritis
Enteropathy- associated arthritis	Vasculitis	
Behçet's disease	Malignancy	
Endocarditis		
Sarcoidosis		
Lyme disease		
Amyloidosis		

NONINFLAMMATORY ARTHRITIS			
Hereditary	Traumatic	Metabolic Disease	Idiopathic
Osteoarthritis (OA) of the hands	OA following local injury	Hemochroma- tosis	
Primary genera- lized OA	OA of the knees in obese patients	Ochronosis	
	Chondromalacia fol- lowing aggressive exercise program	Acromegaly	

Psoriatic Arthritis³

- Joint involvement precedes skin disease in a minority of patients
- Typically has asymmetric involvement
- Frequently involves distal interphalangeal joints
- Associated with “sausage digits”
- Extra-articular manifestations: nail changes such as

pitting, onychodystrophy, onycholysis, transverse depression, brown-yellow discoloration, and leukonychia

Reactive Arthritis⁴

- Systemic illness characterized by aseptic inflammatory joint involvement occurring in a genetically predisposed patient with a bacterial infection localized in a distant organ/system
- *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* are commonly associated infections
- Sacroiliac involvement is often seen in HLA B-27–positive patients
- Predilection for the lower extremities
- Asymmetric involvement
- Extra-articular manifestations: enthesitis, conjunctivitis, skin and mucosal lesions (keratoderma blenorrhagicum, balanitis circinata, ulcerations of the tongue), cervicitis, cystitis, urethritis
- Prognosis: 12%-20% of patients have persistent disease at 2 years

Behçet's Syndrome^{1,2}

- Intermittent, symmetric oligoarthritis of the knees, ankles, hands, or wrists
- Extra-articular manifestations: painful oral and/or genital sores, ophthalmological manifestations (anterior and posterior uveitis, cells in vitreous examination with slit lamp or vasculitis of the retina), erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules, and the combination of stroke and aseptic meningitis

Parvovirus B19 Infection⁵

- Sudden onset of small-joint, symmetric polyarthritis that usually resolves in 2 weeks
- Prominent morning stiffness
- Extra-articular manifestations: typically skin manifes-

tations such as lacy rash, erythema infectiosum, and slapped cheeks

- Female to male ratio: 3-4:1.
- Antibody detection (IgM) may aid in diagnosis

Rheumatoid Arthritis^{1,2}

- Variable presentation with some patients presenting with asymmetric polyarthritis of small joints whereas other patients have an additive arthritis
- Stiffness of joints typically worse in the morning upon awakening or after periods of inactivity
- Vertebral involvement is typically in cervical spine; most commonly occurring at C1-C2
- Extra-articular manifestations: subcutaneous nodules (appear in <50% of the patients), inflammation of the cricoarytenoid joint (manifested by laryngeal pain, dysphonia), interstitial fibrosis, solitary or multiple pulmonary nodules, pericardial effusions, episcleritis, and conjunctivitis sicca
- Felty's syndrome is characterized by RA, splenomegaly, leukopenia, leg ulcers, and thrombocytopenia; most often presents in patients with severe nodule-forming disease
- Rheumatoid factor is positive in 85% of patients

Osteoarthritis^{1,2,6}

- Osteoarthritis (OA) most frequent cause of disability and pain in the elderly
- Pain usually occurs after use of limb and is relieved by rest
- Both hereditary and secondary forms
- Factors leading to secondary OA: excess weight, injury, occupation, anatomic abnormalities, metabolic diseases (hemochromatosis, ochronosis, Wilson's disease, hyperparathyroidism, acromegaly, amyloidosis, Ehlers-Danlos disease)
- Physical examination often reveals coarse crepitus or bony osteophytes

- X-ray confirms diagnosis: classical finding is osteophyte formation or spurs; other features include asymmetric narrowing of the joint space, subchondral bone sclerosis, and cysts with sclerotic walls (in chronic disease)

Diagnostic Studies and Laboratory Values¹

- Tests must be interpreted in the context of the individual patient
- Antinuclear antibody is positive in 5%-10% of the general population and increases with age
- Rheumatoid factor lacks both sensitivity and specificity: positive in 5%-10% of the general population and negative in 20% of RA patients
- Synovial fluid may be useful to confirm the diagnosis of crystal-induced or infectious arthritis
- Other useful laboratory tests: complete blood count, urinalysis (active sediment, proteinuria, or hematuria), serum chemistries (renal failure, liver abnormalities)
- Chest x-ray: may demonstrate infiltrates, nodules, serositis with pleural effusion; fibrosis may be primarily in upper lobes with ankylosing spondylitis but more diffuse with RA, scleroderma, polymyositis

Guide to Acute Management

- Defined by the underlying diagnosis
- Consult Rheumatology for assistance

Psoriatic Arthritis

- Therapeutic approach depends on severity of the arthritis and the presence or absence of axial involvement
- Physical therapy, splints, and exercise are recommended early in the disease
- NSAIDs and intra-articular steroids are useful in mild disease or pauciarticular disease

- Disease-modifying antirheumatic drugs (DMARDs) should be given as soon as possible to patients with erosive polyarticular disease and to those who do not respond to NSAIDs
- DMARDs include methotrexate every week, sulfazalazine (2-3 g/d), and photochemotherapy (PUVA); useful primarily in patients with peripheral arthritis but not in those with axial disease; in small non-controlled trials antimalarials, gold, cyclosporine, mycophenolate mofetil, leflunomide, retinoids, and vitamin D have shown some efficacy
- Etanercept (tumor necrosis factor [TNF] antagonist) shown to improve skin and articular manifestations in patients with poor response to other medications^{7,8}

Reactive Arthritis⁴

- Initiation of therapy is controversial because symptoms typically resolve after weeks or months; only 10%-20% of patients have symptoms 2 years after initial episode
- NSAIDs and intra-articular steroids can be used for symptomatic relief during initial presentation
- No evidence that use of antibiotics decreases duration of symptoms⁹
- For patients with chronic course (>6 months) or evidence of erosions, DMARDs such as sulfasalazine or methotrexate should be used

Behçet's Syndrome

- Aphthous lesions respond to topical or intralesional steroids or dapsone
- Mucocutaneous disease: thalidomide, methotrexate, and colchicines have proved to be effective¹⁰
- Cyclosporine and azathioprine¹¹ useful in management of uveitis; males at greater risk of developing ocular manifestations, so aggressive therapy warranted

Rheumatoid Arthritis

- Major goals of treatment: relieve pain, improve joint function, prevent joint damage and disease-related morbidity and disability
- Occupational and physical therapy should be offered to all patients
- Medications divided into two groups, based on function: (1) control of joint pain and inflammation and (2) decrease further joint damage
- NSAIDs and oral steroids (prednisone 10-20 mg/d tapered over 1-3 weeks) have been used for joint pain and inflammation
- DMARDs are indicated for chronic disease and prevention of further joint damage¹²
- Anti-TNF therapy (etanercept, infliximab, adalimumab) for prevention of further joint erosion/damage

Osteoarthritis

- Nonpharmacological intervention: exercise (range of motion, muscle strengthening, aerobic conditioning), occupational therapy, and weight loss
- Pharmacological therapy: analgesics, anti-inflammatory agents, and/or local steroid injections
- Acetaminophen with ibuprofen and naproxen demonstrated equal efficacy in people with OA of the knee in two clinical trials, but recent surveys of patient preference suggest NSAIDs may have a greater clinical benefit
- Corticosteroid injections: indicated with joint effusion and inflammation; use only two to three times a year because of risk of progressive cartilage damage and pseudo-Charcot arthropathy
- Closed tidal lavage has been reported to benefit patients with knee OA
- Surgery should be considered for patients who fail medical therapy with moderate to severe pain and functional impairment



Patient Care Warnings

- NSAIDs are very efficacious in controlling pain in patients with polyarthritis; however, be aware of possible side effects with continuous use, including renal failure and gastrointestinal bleeding; incidence of these complications increases in the elderly and in patients with prior history of peptic ulcer disease, anticoagulation, or steroid use

References

1. Richie AM, Francis M. Problem-oriented diagnosis: Diagnostic approach to polyarticular joint pain. *Am Family Physician* 2003;68:1151-60.
- 1 2. Sargent JS. Polyarticular arthritis. In Kelley WN, Ruddy S, Harris ED Jr, et al, eds. *Textbook of Rheumatology*, 6th ed. Philadelphia, W.B. Saunders, 2001:379-85.
- 1 3. Boumpas DT, Illei GG, Tassioulas JO. Psoriatic arthritis: Primer on the rheumatic diseases. In Klippel JH, Crofford LJ, Stone JH, et al, eds. *Atlanta, Atlanta Arthritis Foundation*, 2001: 233-37.
- 1 4. Flores D, Marquez J, Garza M, et al. Reactive arthritis: Newer developments. *Rheum Dis Clin North Am* 2003; 29:37-59.
- 1 5. Naides SJ. Infectious Disorders: Viral arthritis. In Klippel JH, Crofford LJ, Stone JH, et al, eds. *Atlanta, Atlanta Arthritis Foundation*, 2001:265-68.
- 1 6. Hochberg MC. Osteoarthritis: Clinical features. In Klippel JH, Crofford LJ, Stone JH, et al, eds. *Atlanta, Atlanta Arthritis Foundation*, 2001:289-92.
- 1 7. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: A randomized trial. *Lancet* 2000;356:385-90.
- 1 8. Leonardi CL, Powers JL, Matheson RT, et al. The etanercept psoriasis study group. *N Engl J Med* 2003;349:2014-22.
- 1 9. Sieper J, Fendler C, Laitko S, et al. No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis: A three-month, multicenter, double-blind, randomized, placebo-controlled study. *Arthritis Rheum* 1999;42:1386-96.
- 3 10. Jorizzo JL, White WL, Wise CM, et al. Low-dose weekly methotrexate for unusual neutrophilic vascular reactions:

Cutaneous polyarteritis nodosa and Behçet's disease. *J Am Acad Dermatol* 1991;24:973-78.

- ② 11. Hamuryudan V, Özyzgan Y, Hizli N, et al. Azathioprine in Behçet's syndrome: Effects on long-term prognosis. *Arthritis Rheum* 1997;40:769-74.
- ③ 12. Matteson EL. Rheumatoid arthritis: Treatment. In Klippel JH, Crofford LJ, Stone JH, et al, eds. *Atlanta, Atlanta Arthritis Foundation*, 2001:225-31.

SYSTEMIC SCLEROSIS

Definition, Etiology, and Epidemiology

- Progressive systemic sclerosis is an incompletely understood disease that targets the skin, lungs, heart, gastrointestinal tract, peripheral circulation, and musculoskeletal system¹
- Characterized by exuberant fibrosis, small vessel vasculopathy, and a prominent autoimmune response
- Incidence in the United States is 19 cases per million per year²
- Female-to-male ratio 7-12:1; female predominance is more pronounced in women of childbearing age
- Life-threatening complications include pulmonary hypertension, aspiration, alveolar hemorrhage (rare), renal crisis and, occasionally, symptomatic pericardial or bowel involvement

Pulmonary Artery Hypertension (PAH)

Definition, Etiology, and Epidemiology

- Pulmonary artery hypertension (PAH) is common among patients with systemic sclerosis, even in the absence of signs and symptoms, and is the leading cause of death of these patients

- PAH more common among patients with limited scleroderma; in autopsy studies, up to 50% of these patients have changes characteristic of PAH, in contrast to 30% of patients who have diffuse disease³
- Progression seems to be predicted by the initial pulmonary pressure and the rate of pressure rise over time

Pearls of the History and Physical Examination^{1,4}

- A third of patients may be asymptomatic
- Dyspnea and fatigue are the most frequent symptoms in patients with right ventricular failure
- Other symptoms include chest pain and syncope during exercise, palpitations, and lower extremity edema
- Jugular venous pulse: prominent A wave due to atrial contraction against a noncompliant ventricle; prominent V wave also observed in the setting of tricuspid regurgitation
- Hepatomegaly, peripheral edema, hypotension, and decreased pulse pressure

Diagnostic Studies and Laboratory Values

- Electrocardiogram: P pulmonale or evidence of right ventricular hypertrophy
- Echocardiogram: may aid in estimation of pulmonary artery pressure and right ventricular function
- Pulmonary catheter placement in all patients with worsening pulmonary hypertension symptoms is advised; three objectives: (1) acquire baseline hemodynamic data, (2) confirm and quantify intracardiac shunt if suspected by echocardiography, (3) evaluate vasoreactivity during vasodilator challenge
- Pulmonary function tests: reduced diffusing capacity of the lung for carbon monoxide below 43% has an 87% sensitivity and specificity for PAH in appropriate clinical setting
- Vasoreactivity in the pulmonary vasculature can be

tested with prostacyclin, adenosine, inhaled nitric oxide, and calcium channel blockers

Guide to Acute Management

Pre-Intensive Care Unit (ICU) Treatment

- Historically, treatment has targeted systemic inflammation; there are only small studies that specifically address treatment of scleroderma
- Cyclophosphamide and prednisone are recommended for patients with pulmonary fibrosis; only anecdotal data are available to support their use for patients with pulmonary disease without pulmonary fibrosis
- Long-term intravenous prostacyclin improves hemodynamic measures, cardiac function, exercise tolerance, and symptoms in patients with New York Heart Association III and IV⁵
- Endothelin-1 receptor antagonist (Bosentan) also approved by FDA for use in these patients
- Retrospective studies suggest that patients on chronic anticoagulation with warfarin (target INR 1.5-3.0) may have better outcomes than patients without anticoagulation

Treatment in the ICU

- The natural history of PAH is that of slow progression over years
- Initial treatment includes oxygen administration, pulmonary vasodilators, cardiac inotropes, and diuretics
- No evidence-based recommendation regarding optimal atrial pressure as a goal for tailored therapy
- Pulmonary artery catheter should be in place, with close monitoring of heart rate (HR) and blood pressure (BP) when assessing for vasoreactivity¹
- Epoprostenol (prostacyclin) guidelines: piggyback the epoprostenol at 1-2 ng/kg/min in a line imme-

diately above the proximal port; titration of 1-2 ng/kg/min should be done every 30 minutes to a maximum of 12 ng/kg/min

- Goals of epoprostenol: decrease in pulmonary pressure by 10% and increase in cardiac output of 30%
- Decrease in BP of $>40\%$; increase in HR $>40\%$; side effects such as headache, nausea, vomiting, lightheadedness, and severe anxiety are indications for termination of infusion of epoprostenol
- Inhaled nitric oxide (iNO) can be given in patients with acute decompensation, having a low risk for systemic hypotension
 - NO guidelines: set up an aerosol face mask to a standard aerosol nebulizer device with a flow rate of 10 L/min; set up Venturi device to keep $\text{SpO}_2 >92\%$; insert corrugated tubing horns into de-exhalation side ports on the aerosol mask to create a gas reservoir; place flow transducer and gas injector of the iNO vent in line with nebulizer, device, and patient; obtain baseline hemodynamics; begin iNO at 0.5 ppm and measure hemodynamics every 10 minutes; increase iNO to 1, 2, 5, 10 ppm at 10-minute intervals
 - Target hemodynamics are the same as for epoprostenol; measure NO or methemoglobin levels if symptoms develop
- If hemodynamic targets are achieved during vasodilator challenge, calcium channel blockers or other long-term medications can be started
- Digoxin can be given to prevent the negative inotropic effect of calcium channel blockers in patients with pulmonary hypertension and symptomatic heart failure associated with this class of medications
- Atrial septostomy may improve symptoms in patients with end-stage disease, although severe hypoxemia secondary to intracardiac shunt may occur⁶



Patient Care Warnings

- PAH is a frequent complication of systemic sclerosis, even with subclinical disease
- Patients are very susceptible to hypotension; if antihypertensives and diuretics are to be given or if patients are to be started on a trial of vasodilators, close monitoring of hemodynamic parameters is necessary

Renal Crisis

Definition, Etiology, and Epidemiology

- Defined as the acute onset of accelerated arterial hypertension or rapidly progressive oliguric renal dysfunction in the course of systemic sclerosis⁷
- In the last 10-15 years the outcome of scleroderma renal crisis has improved dramatically with the use of angiotensin-converting enzyme inhibitors (ACEi)
- Occurs in 10% of patients with scleroderma, with the greatest risk in patients with diffuse disease (up to 25% of patients)⁷
- Risk factors for renal crisis include: first 3-4 years of disease, black, and male gender
- One of the best predictors for development of renal crisis is the rate of progression of skin thickening; other predictors include diffuse skin involvement, presence of anti-RNA polymerase III antibody, anemia, pericardial effusions, congestive heart failure, and antecedent use of high-dose corticosteroids

Pearls of the History and Physical Examination

- Assess for recent steroid use, duration of the disease, time of progression, new onset seizures,

headache, blurry vision, presence of hematuria, and volume overload symptoms

- On physical examination: papilledema is observed in 8% of patients; volume overload; BP is commonly $>150/90$ mm Hg, with frequent diastolic pressures >120 mm Hg; rarely, normal BP can be seen in the setting of renal crisis

Diagnostic Studies and Laboratory Values⁷

- Urinalysis: microscopic hematuria is frequent (38%), granular casts (29%)
- Creatinine usually increases 0.5-1.0 mg/dL/d
- Hematology: microangiopathic hemolytic anemia, thrombocytopenia, and reticulocytosis occur in 43% of patients
- Hyperreninemia is the hallmark of renal crisis, although its usefulness is limited due to result delays and measurement interference associated with ACEi use
- Erythrocyte sedimentation rate >25 mm/hr
- Pericardial effusions are seen in echocardiograms in 53% of patients

Guide to Acute Management

- Prior to ACEi this entity was fatal due to a vicious cycle of decreased blood flow, cortical ischemia, hyperreninemia, hypertension, and further vasoconstriction
- ACEi is the cornerstone of treatment: first used in the late 1970s with a dramatic improvement in 1-year survival from less than 10% to 65%; more recent data show up to 90% of patients are still alive at 5 years⁸
- Aggressive blood pressure control and dialysis are also integral aspects of supportive therapy

- Poor prognostic factors: creatinine >3 mg/dL at time of diagnosis, older age, male gender, congestive heart failure symptoms, and elevated BP after 3 days of treatment²



Patient Care Warnings

- Always use ACEi, even during dialysis, as it improves the outcome of these patients
- Patients with scleroderma renal crisis may not be hypertensive during initial evaluation, but this does not exclude the diagnosis⁹
- Early treatment with ACEi is the most important predictor of final outcome

References

- ③ 1. Cossio M, et al. Life-threatening complications of systemic sclerosis. *Crit Care Clin* 2002;18:819-39.
- ③ 2. Maricq HR, Weinrich MC, Keil JE, et al. Prevalence of scleroderma spectrum disorders in the general population of South Carolina. *Arthritis Rheum* 1989;32:998-1006.
- ③ 3. Battle RW, Davitt MA, Cooper SM, et al. Prevalence of pulmonary hypertension in limited and diffuse scleroderma. *Chest* 1996;110:1515-19.
- ③ 4. Wigley FM. Systemic sclerosis and related syndromes: Clinical features. *Primer on the rheumatic diseases*. In Klippel JH, Crofford LJ, Stone JH, et al, eds. Atlanta, Atlanta Arthritis Foundation, 2001:357-64.
- ① 5. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to scleroderma spectrum disease: A randomized, controlled trial. *Ann Intern Med* 2000;132:425-34.
- ③ 6. Allock RJ, O'Sullivan JJ, Corris PA. Palliation of systemic sclerosis-associated pulmonary hypertension by atrial septostomy. *Arthritis Rheum* 2001;44:1660-62.
- ③ 7. Steen VD. Scleroderma renal crisis. *Rheum Dis Clin North Am* 2003;29:315-33.
- ② 8. Steen VD, Medsger TA. Long-term outcomes of scleroderma renal crisis. *Ann Intern Med* 2000;133:600-03.
- ③ 9. Helfrich DJ, Banner B, Steen VD, et al. Normotensive renal failure in systemic sclerosis. *Arthritis Rheum* 1989;32:1128-34.

ENDOCRINOLOGY

DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR STATE

Definition, Etiology, and Epidemiology

- Diabetic ketoacidosis (DKA) is the result of overproduction and accumulation of acetoacetic acid and β -hydroxybutyric acids, the “ketone bodies”; this is primarily due to insulin deficiency coupled with glucagon excess; counterregulatory hormones such as epinephrine/norepinephrine, growth hormone, and hydrocortisone also play ancillary roles¹
- Volume depletion and ketoacidosis are the hallmark features
- Initial presentation of type 1 diabetes mellitus in approximately 25%-40% of children and adolescents diagnosed with DKA¹; accounts for 100,000 hospitalizations per year in all age groups
- Precipitating factors include cessation or mismanagement of insulin therapy or concurrent illnesses: most common infection is pneumonia or urinary tract infection; otherwise, alcohol or drug use, myocardial infarction, volume depletion, pancreatitis, trauma²; in many cases there is no apparent precipitating event
- Mortality rate in adults less than 5% with proper management; death usually due to complications listed below, including myocardial infarction or stroke; cerebral edema is the most common cause of death in children

Pearls of the History and Physical Examination

- DKA presents with vomiting, dehydration, shortness of breath, abdominal pain, or alterations in levels of consciousness associated with an antecedent history of polyuria, polydipsia, weight loss, change in appetite, or decrease in activity
- Kussmaul breathing indicates severe acidosis

LEVELS OF SEVERITY ¹				
Severity	HCO ₃	pH	Volume Depletion	Vomiting
Ketosis	≥20 mEq/L	>7.35	None to mild	No
Mild DKA	15-20 mEq/L	7.30-7.35	Mild; compensated	Usually No
Moderate DKA	10-15 mEq/L	7.2-7.3	Moderate; clinical apparent	Common
Severe DKA	<10 mEq/L	<7.2	Usually >7%-10%	Frequent

Diagnostic Studies and Laboratory Values³

- Obtain and monitor vital signs
- Bedside glucose measurement every 30-60 minutes (see below for parameters)
- Obtain urine sample for glucose and ketones
- Laboratory tests: serum electrolytes, blood urea nitrogen, complete blood count, and arterial blood gas; triglycerides, amylase, and lipase for concurrent or precipitating pancreatitis
- Drug screen to assess for precipitating factors
- Chest x-ray and urine and blood culture if clinical suspicion for infection; fever may be better indicator for infection than leukocytosis as DKA can cause a leukemoid reaction in the absence of infection.

Management Principles of Severe DKA^{1,2}

- Evaluate for and treat underlying condition as well as manage hyperglycemia, electrolyte repletion, and volume resuscitation

Insulin

- Initial loading dose of 15-25 units (U) of regular insulin
- Continuous intravenous (IV) infusion at 0.1 U/kg/hr of regular insulin
- Use the anion gap to follow progress in therapy; if anion gap has not narrowed after 4 hours of therapy, insulin infusion can be increased up to 0.15-0.20 U/kg/hr

Dextrose

- Should be adjusted with a D5% or D10% IV solution to maintain glucose above 250 mg/dL to minimize risk of cerebral edema

Fluids and Electrolytes

- Net average volume deficit is 3-5 L of normal saline; the initial fluid bolus should be given rapidly, especially if the patient presents with hypotension (10-20 mL/kg fluid bolus of isotonic fluid)
- Further replacement fluids can be delivered at a rate of 1.5-2.0 times maintenance rate and can be guided by urine output and blood pressure
- Replete K⁺ even if patient known to be normo- or hypokalemic on presentation as patients are total body potassium-depleted; most patients are hyperkalemic on presentation secondary to extracellular shift caused by the acidosis but are still to be considered potassium-depleted

- In the hypokalemic patient, insulin injection can be delayed while potassium-repleted to avoid intracellular shift of potassium that may lead to worsening hypokalemia and arrhythmias
- Acidosis may render vasculature less responsive to catecholamines; in the hypotensive patient with a pH <7.0, bicarbonate infusions may be given initially over the first 2 hours; bicarbonate does not have a role in other situations, or simply to correct acidosis, because it may cause paradoxical central nervous system acidosis, hypokalemia, hypertonicity secondary to excessive sodium load, and increase risk of cerebral edema

Complications of DKA^{1,4}

- Cerebral edema (restricted to children)
- Myocardial infarction
- Adult respiratory distress syndrome
- Thrombosis/disseminated intravascular coagulation
- Neurological complications: hematoma, infarction, cerebral venous thrombosis, optic atrophy, hydrocephalus, meningeal syndrome
- Pulmonary: aspiration pneumonia, pulmonary edema, pulmonary embolism, pneumomediastinum
- Rhinocerebral mucormycosis
- Rhabdomyolysis

HYPERGLYCEMIC HYPEROSMOLAR COMA (HHC)

Definition

- HHC is a complication of type 2 diabetes mellitus; it is a syndrome of unrelenting osmotic diuresis

without sufficient repletion of water by the patient

Criteria and Clinical Findings⁵

- Plasma glucose concentration >600 mg/dL (typically closer to 1000 mg/dL)
- Plasma bicarbonate >15 mmol/L (typically >20 mmol/L; if below 10 mmol/L, consider measuring blood lactate); lactic acidosis may be from volume depletion or concurrent sepsis
- Small ketonuria
- Absent to low ketonemia
- Serum osmolality >320 mOsm/kg
- Severe volume depletion (average net deficiency ~ 11 L)
- Patients with type 2 diabetes mellitus are resistant to ketone body formation and therefore may not present with nausea, vomiting, and abdominal pain; patients often do not realize they are seriously ill
- Depressed level of consciousness, even stupor or coma

Guide to Acute Management

- Patients with HHC are treated similarly to those with DKA, which includes volume repletion, insulin administration, and electrolyte replacement; generally require more fluids and less insulin
- 0.9% of normal saline should be used for fluid resuscitation as they are usually more volume-depleted than DKA patients; consider changing to 0.45% saline once volume replete
- Patients have to be evaluated for any precipitating factors mentioned above, such as infection



Patient Care Warnings

- Important to evaluate for and treat the underlying cause for DKA or hyperosmolar coma; not always secondary to medical noncompliance; infection is common in both conditions, and genitourinary causes and perirectal abscesses are often missed on initial evaluation
- Consider intensive care unit–level care for severe DKA
- Intubation is rarely required and should be avoided even in severe DKA; difficult to maintain minute ventilation requirements of patients with DKA and may cause concurrent respiratory acidosis

References

- ③ 1. White NH. Management of diabetic ketoacidosis. *Rev Endocrinol Metab Dis* 2003;4:343-53.
- ③ 2. Ilag LL, Kronick S, Ernst RD, et al. Impact of a critical pathway on inpatient management of diabetic ketoacidosis. *Diabetes Res Clin Pract* 2003;62:23-32.
- ③ 3. Kaufman FR. Type 1 diabetes mellitus. *Pediatr Rev* 2003;24:291-300.
- ③ 4. Nathan DM. Long-term complications of diabetes mellitus. *New Engl J Med* 1993;328:1676-85.
- ③ 5. Morales AE, Rosenbloom AL. Death caused by hyperglycemic hyperosmolar state at the onset of type 2 diabetes. *J Pediatr* 2004;144:270-73.

THYROID DISEASE

Definition, Etiology, and Epidemiology

- Thyroid diseases are classified, according to the total bound and free level of circulating thyroid hormones, as euthyroid, hyperthyroid, or hypothyroid

- Affect 5% of the adult population in the United States, occurring at a rate of 60-80 per 1000 adults^{1,2}
- Female population has 10% incidence of thyroid disorders versus 2% for males
- Most common cause of thyroid disease worldwide is iodine deficiency, in contrast to the United States, where it is autoimmunity^{1,3}

Hyperthyroidism

Definition, Etiology, and Epidemiology

- Hyperthyroidism is a hypermetabolic state that occurs due to excessive circulating and intracellular thyroid hormones
- Most common causes: Graves' disease (60%-90%), silent and postpartum thyroiditis, toxic multinodular goiter, autonomous functioning adenoma, and exogenous thyroid hormone ingestion⁴
- Other causes include high iodine load (i.e., amiodarone use), trophoblastic disease or germ-cell tumors, and thyrotropin-releasing hormone (TSH) pituitary tumors⁵
- Graves' disease is identified by thyrotoxicosis associated with development of a goiter, ophthalmopathy, local myxedema, and acropachy (soft-tissue swelling of hands and feet)
- Thyroid storm is a syndrome of severe thyrotoxicosis usually precipitated by an infection that may result in organ system failure and is associated with significant mortality rates

Pearls of the History and Physical Examination

- Tremor, anxiety, warm/moist skin, proptosis, tachycardia, wide pulse pressure, and systolic hypertension^{1,2}

- Elderly population can present with cardiovascular dysfunction (i.e., atrial fibrillation), dyspnea, weight loss, and proximal muscle weakness
- Painful and tender neck associated with fever, malaise, and sore throat are characteristic of subacute thyroiditis (de Quervain's thyroiditis)²
- Thyroid storm represents exaggerated hyperthyroidism and presents with fever ($>102^{\circ}\text{F}$), tachycardia, gastrointestinal dysfunction (nausea, vomiting, diarrhea, jaundice), and dysfunction of the central nervous system (hyperirritability, anxiety, confusion, apathy, coma)⁶; this severe and life-threatening thyrotoxic state is an endocrinological emergency.

Diagnostic Studies and Laboratory Values

- Laboratory tests: increased free thyroxine (T₄) or free triiodothyronine (T₃) (usually rises first), suppressed thyroid-stimulating hormone (TSH typically <0.01 mU/L), elevated ionized calcium, decreased total cholesterol, and elevated alkaline phosphatase^{1,2}
- TSH receptor-stimulator antibody (or thyroid stimulating immunoglobulin [TSI]) positivity is suggestive of Graves' disease
- High erythrocyte sedimentation rate: subacute thyroiditis
- If hyperthyroidism is associated with high TSH, consider pituitary adenoma or selective pituitary resistance state as part of the differential
- Radioactive isotope imaging of thyroid gland: increased uptake in most thyrotoxic states, except in subacute thyroiditis and exogenous thyroid hormone ingestion where there is decreased uptake

Guide for Acute Management

- Beta-adrenergic blocking agents (propranolol, metoprolol) to decrease symptoms until free T₄ or T₃ levels returned to normal range

- Anti-thyroid medications: either propylthiouracil (PTU) or methimazole; PTU has the additional benefit of inhibiting peripheral conversion of T₄ to T₃ and is the preferred agent in pregnancy; choice between the two agents is typically a personal preference, but methimazole has once-a-day dosing leading to better adherence, and side effects tend to be dose-related, which is not the case with PTU
 - Methimazole dose in overt hyperthyroidism (nonthyroid storm): start 5-20 mg orally po every 8 hours until euthyroid, then start maintenance dose 5-15 mg po every day
 - PTU in overt hyperthyroidism: 300-450 mg po every day in divided doses every 6 hours
- Other therapies include: acetaminophen (for fever), fluids with D5 or D10 normal saline and steroids
- Thyrotoxicosis due to subacute thyroiditis: treat symptoms and give nonsteroidal anti-inflammatory drugs (NSAIDs); consider adding short course of steroids if pain is severe
- Symptoms should improve in 12-24 hours
- Thyroid storm⁶: therapeutic options are the same as for uncomplicated hyperthyroidism except doses are higher and given more frequently
 - Beta blockers (propranolol or esmolol) to decrease adrenergic tone; propranolol can be given intravenously (1 mg/min)
- Methimazole 30 mg every 6 hours or PTU 200 mg every 4 hours po or rectally; PTU used traditionally in hospitalized patients, given effect on peripheral conversion of T₄ to T₃
- Iodine-containing solutions to block release of T₄ and T₃
- Glucocorticoids for inhibition of conversion of T₄ to T₃; typically can give hydrocortisone 100 mg intravenously in severe thyroid storm

Hypothyroidism

Definition, Etiology, and Epidemiology

- Occurs in 1%-2% of the general population; 14 times more common in women²
- Most common causes of primary hypothyroidism include autoimmune thyroiditis (Hashimoto's thyroiditis), iodine deficiency, and silent and postpartum thyroiditis¹
- If hypothyroidism is found to be secondary, then panhypopituitarism should be ruled out
- Major drugs causing hypothyroidism include lithium and amiodarone³
- Thyroid hormone affects almost every organ system, including cardiovascular, gastrointestinal, integument, musculoskeletal, hemopoietic, endocrine, and neuropsychiatric^{2,3}

Pearls of the History and Physical Examination

- Scaly skin, alopecia, brittle hair and nails, cardiovascular disturbances (decreased systolic blood pressure, increased diastolic blood pressure, bradycardia, pericardial effusion, torsade de pointes), constipation, dysphagia, anemia, galactorrhea, inability to concentrate, depression, and sleep apnea
- Elderly population can present with depression and dementia
- Myxedema coma: hypothermia and altered mental status are hallmark features; can also present with hypoglycemia, hypotension, hyponatremia, hypoventilation, bradycardia, and seizures

Diagnostic Studies and Laboratory Values

- Low free T₄, low T₃, and TSH >20 mU/L
- Low T₄, low T₃, and low TSH can be observed in

secondary hypothyroidism and euthyroid sick syndrome

- Presence of anti-thyroid peroxidase and anti-thyroglobulin antibodies in Hashimoto's thyroiditis

Guide to Acute Management

- Administration of levothyroxine replacement following levels of T₄, which often takes 1-2 weeks to reach a steady state
- T₄ is a prohormone that is converted to the active hormone T₃
- Approximately 80% of the T₄ administered is absorbed and has a long half-life (7 days), resulting in nearly constant T₃ levels when steady state achieved
- Typical starting dose in patients without myxedema coma is 25-50 µg po daily with standard maintenance doses approximating 1.6 µg/kg/d
- Conservative treatment as thyroid replacement therapy for elderly patients and those with known coronary artery disease or increased risk of arrhythmia can increase myocardial oxygen demand and induce angina/arrhythmia
- TSH will typically return to normal limits (0.5-5.0 mU/L) in 6-8 weeks
- Myxedema coma is an endocrine emergency and should be treated aggressively before diagnosis is confirmed
 - Begin IV thyroxine with loading dose 200-400 µg followed by daily doses of 50-100 µg with both doses depending on weight and cardiac risk factors
 - Intravenous T₃ has also been used, given shorter onset of activity with initial loading dose 10-20 µg, followed by 10 µg every 4 hours for the first 24 hours, then every 6 hours for the next 48 hours⁷
 - Some authorities prefer combination of T₄ and T₃⁷

- No evidence exists regarding improved efficacy (or safety) of any one of these approaches to replacement therapy⁶; however, most experts recommend monotherapy with T₄
- Until coexisting adrenal insufficiency is ruled out, must treat with concurrent stress-dose corticosteroids
- Supportive measures include passive rewarming (heating blanket), correction of hyponatremia, empiric antibiotics



Patient Care Warnings

- NSAIDs and salicylates should be avoided during thyrotoxic states, other than subacute thyroiditis, as they will compete with thyroid hormones binding sites on transport proteins
- If patient presents with atrial flutter, supraventricular tachycardia, and/or premature ventricular complexes, suspect coronary artery disease
- Pregnancy will increase thyroid-binding globulin levels, decreased free T₄, and free T₃, and will deplete iodine stores, so dose of levothyroxine should be increased to avoid overt hypothyroidism
- Monitor closely with dopamine, glucocorticoids, and octreotide use, as these agents may cause decreased TSH secretion⁸
- Lithium and other iodine-containing medications can cause decreased secretion of thyroid hormones, resulting in hypothyroidism⁸
- In myxedema coma, treat with corticosteroids until coexisting adrenal insufficiency is ruled out

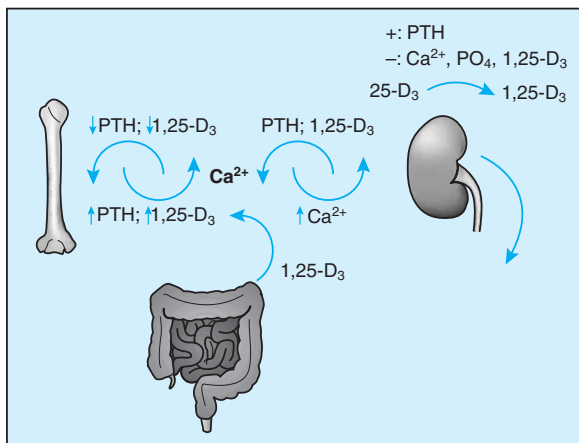
References

- ③ 1. Weetman AP. Graves' disease. *New Engl J Med* 2000;343:1236-48.
- ③ 2. Wilson GR. Thyroid disorders. *Clin Family Pract* 2002;4.
- ③ 3. Roberts CG, Landenson PW. Hypothyroidism. *Lancet* 2004;363:793-803.
- ③ 4. Monaco F. Classification of thyroid diseases: Suggestions for a revision. *J Clin Endocrinol Metab* 2003;88:1428-32.
- ③ 5. Evans TC. Thyroid disease: Primary care. *Clin Office Pract* 2003;30.
- ③ 6. Sarlis NJ, Gourgiotis L. Thyroid emergencies. *Rev Endocrinol Metab Disorder* 2003;2:129-36.
- ③ 7. Wartofsky L. Myxedema coma. In Braverman LE, Utiger RE, eds. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*. Philadelphia, Lippincott Williams & Wilkins, 2000:843-47.
- ③ 8. Surks MI. Drugs and thyroid function. *New Engl J Med* 1995;333:1688-94.

CALCIUM HOMEOSTASIS

Definition, Etiology, and Epidemiology¹⁻³

- Of body calcium, 99% resides in bone; only 1% is extracellular: half is ionized, and the remainder is bound to protein (albumin) or complexed to anions (sulfate, citrate, etc); only ionized calcium is physiologically active and regulated
 - Changes in protein can markedly affect total serum calcium levels
 - Plasma pH mildly affects ionized calcium levels via protein binding (increased binding in alkalosis, decreased binding in acidosis)
- Calcium homeostasis is set by flux across gut, bone, and kidney under the regulation of two key hormones: parathyroid hormone (PTH) and 1,25-dihydroxy-vitamin D (1,25(OH)₂ D).
- Major actions of PTH:
 - Inhibits phosphate reabsorption in proximal tubule



Modified from Miedlich S, Krohn K, Paschke R. Update on genetic and clinical aspects of primary hyperparathyroidism. Clin Endocrinol 2003;59:539-54.

- Increases production of $1,25(\text{OH})_2 \text{D}$ in kidney
- Enhances reabsorption of calcium in distal tubule
 - 65% of calcium is reabsorbed passively in the proximal convoluted tubule
 - 10%-20% reabsorbed in thick ascending limb of Henle due to luminal gradient generated by Na-K-Cl_2 transport (site of furosemide inhibition)
 - 10% actively absorbed in distal convoluted tubule coupled to Na-Cl transport (site of thiazide diuretics); potential mechanism includes PTH activity on the principal cell ($\uparrow$ basolateral exit of $\text{Cl} \rightarrow \uparrow$ conductance of Cl across cell $\rightarrow \uparrow$ calcium influx)
- Increases bone resorption to mobilize calcium
 - Major regulator of PTH secretion is ionized calcium: tightly coupled sigmoid dose-response curve
 - Elevated PO_4 stimulates PTH by lowering calcium and $1,25(\text{OH})_2 \text{D}$ levels; major mechanism in secondary hyperparathyroidism observed in end-stage renal disease (ESRD)
- Major actions of $1,25(\text{OH})_2 \text{D}$
 - Increased absorption of calcium from the gut; passive absorption is low-efficiency; significant

absorption requires vitamin D-dependent calcium channel

- Excess observed with excess ingestion (vitamin D intoxication) or ectopic (extrarenal) production of $1,25(\text{OH})_2 \text{D}$ (granulomatous states)
- Increased resorption of bone in conjunction with PTH
- Hypercalcemia is much more common than hypocalcemia; leading cause in the general population (outpatient setting) is primary hyperparathyroidism (90%); most common cause in inpatients is hypercalcemia of malignancy (50%), with primary hyperparathyroidism being second most common cause

Differential for Disorders of Calcium Homeostasis¹⁻⁴

HYPERCALCEMIA		
Excess Bone Resorption	Excess Influx from Gut	Decreased Excretion
Hypercalcemia of malignancy • Local osteolytic: myeloma, breast, lung • Humoral (PTHrP): most common in lung, breast, squamous cell, renal cell, and bladder cancers • Extrarenal $1,25(\text{OH})_2 \text{D}$ production (lymphoma) Hyperparathyroidism • Primary • Adenoma (85%), hyperplasia (15%), carcinoma (1%), Multiple endocrine neoplasia (MEN1 or 2a) (1%-2%) Immobilization Hyperthyroidism: mild; direct effect of thyroxine on bone resorption	Vitamin D intoxication Granulomatous disease (tuberculosis, sarcoid) Milk-alkali syndrome	Thiazide diuretic use Lithium toxicity Familial hypocalciuric hypercalcemia (FHH) (inactivating mutation in calcium-sensing receptor)

HYPOCALCEMIA

Increased Calcium Losses/Deposition	Decreased Calcium Resorption/Absorption	Other
Excess binding of calcium	Decreased bone resorption: often drug-induced (mithramycin, bisphosphonates, phosphates)	Hypoalbuminemia (falsely low total calcium concentration)
Acute pancreatitis (saponification)	Hypomagnesemia	Pseudohypocalcemia (transiently from gadolinium)
Rhabdomyolysis/tumor lysis syndrome (release of cellular PO_4 complexing with calcium)	Hypoparathyroidism	
Blood transfusions (citrate complexes with calcium with impaired citrate clearance secondary to hepatic or renal disease)	Acquired: surgical	
Other chelators: ethylenediaminetetraacetic acid, foscarnet	Autoimmune	
Extravascular deposition: Hyperphosphatemia especially in setting of ESRD	Congenital: DiGeorge's syndrome, familial	
Lactic acidosis	Pseudohypoparathyroidism (target cell resistance to PTH)	
Sepsis	Decreased gut absorption: vitamin D deficiency	
Hungry bone syndrome	Nutritional	
	Malabsorption states	
	Inadequate sun exposure	
	Genetic: vitamin D resistance states (type 1 and type 2)	

Pearls of the History and Physical Examination

Hypercalcemia^{1,5}

- Most common complaints: constipation, nausea/vomiting, diffuse abdominal pain, and generalized weakness; polyuria and polydipsia occur due to decreased renal tubular concentrating ability
- Symptoms related to extent and duration of hypercalcemia
- Depressed mental status or confusion at higher calcium levels

- Classic complications of hyperparathyroidism include nephrolithiasis, bone pain, fracture (“stones, groans, bones, and psychic moans”)
- Shortens QT by shortening myocardial action potential, usually without clinical effect; rarely are atrioventricular block and bradycardia observed; long-term hypercalcemia can cause calcification of myocardial fibers, valves, vessels, and conduction system
- Pearls of history-taking: check for vitamin D, vitamin A, thiazide, calcium carbonate (Tums) use, immobilization, volume status, and possible occult malignancy

Hypocalcemia

- Most common symptoms are of neuromuscular irritability: paresthesias (perioral, fingertips/toes), muscle cramps, proximal myopathy
- Prolonged QT can be significant as well as bradycardia and heart block
- Seizures (tetany), occasionally with laryngeal spasm
- Physical examination: Chvostek’s sign (facial twitch with tapping over facial nerve), Trousseau’s sign (carpal spasm with inflation of blood pressure cuff on arm for 3 minutes)
- Pearls of history-taking: look for use of phosphate binders (especially with aluminum) in dialysis patients, prior neck surgery, medication list

Diagnostic Studies and Laboratory Values

- Serum calcium, phosphorous, albumin, creatinine, $\pm$ ionized calcium and magnesium
 - Corrected calcium = serum calcium + 0.8 (4 - serum albumin)
 - In acidosis, for every decrease of 0.1 in pH, ionized Ca^{+} rises by 0.2 mg/dL
 - Marked hypomagnesemia causes hypocalcemia

- PTH (intact hormone 1-84 assay)
- Vitamin D [(25-(OH)D and 1,25-(OH)₂D]
 - 25(OH)D is best measure of vitamin D stores; use to assess for vitamin D deficiency; 1,25(OH)₂D is elevated in granulomatous diseases
 - 1 α -hydroxylation occurs in kidney; induced by PTH and low PO₄; repressed by calcium and 1,25(OH)₂D; thus reduced, 1,25(OH)₂D concentrations can be significant in renal disease
 - 1 α -hydroxylase also found in other tissues, notably granulomata and activated macrophages
- Urinary calcium
 - Normal 24-hour urinary excretion of calcium ranges 100-200 mg
 - Fractional excretion of calcium (FCa²⁺) <1% in FHH
 - Hypercalciuria observed with primary hyperparathyroidism or renal calcium leak
- Serum protein electrophoresis and urine electrophoresis to assess for multiple myeloma as cause of hypercalcemia
- Parathyroid hormone-related protein to assess for humoral hypercalcemia of malignancy (most commonly with lung, breast, squamous cell, renal cell, and bladder cancers) or if suspicion of occult malignancy

Guide to Acute Management

Hypercalcemia

- Volume repletion with normal saline is the first and key step in initial management; hypercalcemia causes volume contraction, which in turn further exacerbates increased serum calcium levels
- Forced diuresis with low-dose furosemide (with intravenous [IV] fluid) can enhance renal calcium excretion; do not cause volume contraction: produces mild to modest drop in calcium

- Bisphosphonates effective for treatment especially in setting of malignancy; act to inhibit osteoclast activity; require 24-48 hours for peak onset of action; most data support the use of:
 - Pamidronate 60-90 mg IV⁶
 - Zoledronic acid 4 mg IV^{7,8}
- Calcitonin (4 IU/kg every 12 hours SC or IM $\times$ 1-2 days) useful to rapidly lower serum calcium; ineffective for long-term therapy due to development of tachyphylaxis
- Glucocorticoids (e.g., prednisone 20-40 mg daily) in cases of vitamin D-mediated hypercalcemia (lymphoma or granulomatous disease)
- Dialysis indicated for severe hypercalcemia specifically in patients with renal failure or congestive heart failure when large volume shifts not well tolerated

Hypocalcemia

- Oral calcium and vitamin D supplementation for chronic hypocalcemia
 - 1-3 g/d elemental calcium in 3-4 divided doses with meals is often required
 - With vitamin D or PTH deficiency can give calcitriol starting at 0.25 μ g po daily
- For acute symptomatic hypocalcemia: IV calcium gluconate at 1-2 mg/kg/hr (mix 6 ampules calcium gluconate in 500 mL D5 to give $\sim$ 1 mg/mL); may require bolus of up to 4 mg/kg over 15 minutes for initial therapy for severe hypocalcemia; goal is to gradually raise calcium to low to normal range
- Telemetry monitoring, especially if electrocardiogram changes noted with hypocalcemia
- If hyperphosphatemia is the cause of hypocalcemia, goal is to decrease phosphate rather than replace calcium; high PO_4 :

- Decreases $1,25(\text{OH})_2\text{D}$ production
- Inhibits bone resorption of Ca^{2+}
- Complexes with calcium; $\text{Ca} \times \text{PO}_4$ product $> 55 \uparrow$ risk for calciphylaxis (spontaneous tissue precipitation in skin, muscle, myocardium)



Patient Care Warnings

- Avoid IV calcium chloride and favor calcium gluconate when possible due to the risk of chemical injury
- Remember that the effect of IV calcium is transient and not always benign; for chronic hypocalcemia, repletion of calcium stores must be done with oral therapy with calcium plus vitamin D
- In acute hypercalcemia, always correct volume status first as this exacerbates hypercalcemia; do not give Lasix without adequate hydration
- Bisphosphonates require 24-48 hours to affect calcium levels; to acutely lower calcium levels, volume replete first, then use loop diuretics and calcitonin if hypercalcemia remains severe

References

- ③ 1. Body J, Bouillon R. Emergencies of calcium homeostasis. *Rev Endoc Metab Dis* 2003;4:167-75.
- ③ 2. Marx SJ. Hyperparathyroid and hypoparathyroid disorders. *N Engl J Med* 2000;343:1863-75.
- ③ 3. Miedlich S, Krohn K, Paschke R. Update on genetic and clinical aspects of primary hyperparathyroidism. *Clin Endocrinol* 2003;59:539-54.
- ③ 4. Carlstedt F, Lind L. Hypocalcemic syndromes. *Crit Care Clin* 2001;17:139-53.

- ③ 5. Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992;326:1196-1203.
- ② 6. Nussbaum SR, et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: Comparison of 30-, 60-, and 90-mg dosages. *Am J Med* 1993;95:297-304.
- ① 7. Berenson JR, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001 Apr 1;91:1191-1200.
- ① 8. Rosen LS, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase III, double-blind, randomized trial. The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21:3150-57.

ADRENAL INSUFFICIENCY

Definition, Etiology, and Epidemiology¹

Primary Adrenal Insufficiency

- Dysfunction at the level of the adrenal glands from: impaired steroidogenesis, glandular destruction, or dysgenesis/hypoplasia
- Relatively uncommon; incidence 93-140 per million; age at diagnosis peaks in fourth decade of life; women more frequently affected than men
- 70%-90% autoimmune in etiology (75% associated with autoantibodies to enzymes such as 21-hydroxylase); classical Addison's disease is primary autoimmune adrenalitis
- The adrenal gland is the most common endocrine organ affected by HIV; increased incidence of adrenal insufficiency in HIV patients due to multiple factors: disturbances of the hypothalamo-pituitary-adrenal-axis, relative peripheral glucocorticoid resistance, infiltrative opportunistic infections (see following table), and effects of antiretroviral and other drugs (e.g., rifampin, ketoconazole, megestrol acetate)²

ETIOLOGIES OF PRIMARY ADRENAL INSUFFICIENCY^{1,3}

Infectious	Hemorrhagic	Infiltrative	Drug-Related	Autoimmune	Genetic/Congenital (Rare)
Tuberculosis	Waterhouse-Friedrichsen syndrome with meningococcal or pseudomonal infection (sepsis with DIC)	Amyloidosis	Inhibit steroid synthesis:	(Isolated) autoimmune adrenalitis	Congenital adrenal hyperplasia (classic 21-OH deficiency)
Fungal disease		Sarcoidosis	Etomidate,	Autoimmune polyglandular syndrome:	Congenital adrenal hypoplasia
Histoplasmosis		Hemochromatosis	Ketoconazole, Mitotane	Type I: adrenalitis, hypoparathyroidism, mucocutaneous candidiasis	Adrenoleukodystrophy
Coccidiomycosis	Antiphospholipid syndrome	Metastases	Increase steroid catabolism:	Type II (Schmidt's syndrome): adrenalitis, thyroiditis, type I diabetes	Adrenomyeloneuropathy
Cryptococcus	Anticoagulation (heparin, warfarin)	Lung, breast most common	phenytoin, phenobarbital, rifampin		Familial glucocorticoid deficiency
Cytomegalovirus		Lymphoma, melanoma			
Kaposi's sarcoma (HHV-8)					

ETIOLOGIES OF SECONDARY ADRENAL INSUFFICIENCY

Infiltrative	Hemorrhagic/ Necrotic	Iatrogenic/ Traumatic	Autoimmune	Neoplastic	Other
Hemochromatosis	Pituitary apoplexy	Postsurgical	Lymphocytic hypophysitis	Craniopharyngioma	Empty sella syndrome
Sarcoidosis	Sheehan's syndrome (postpar- tum infarction with pituitary necrosis)	Postradiation		Pituitary adenoma/carcinoma	Isolated adreno- corticotrophic hor- mone (ACTH) deficiency
Amyloidosis		Head trauma with skull fracture			Exogenous corti- costeroid therapy
Histiocytosis					Hypothalamic/ pituitary disease

Secondary Adrenal Insufficiency

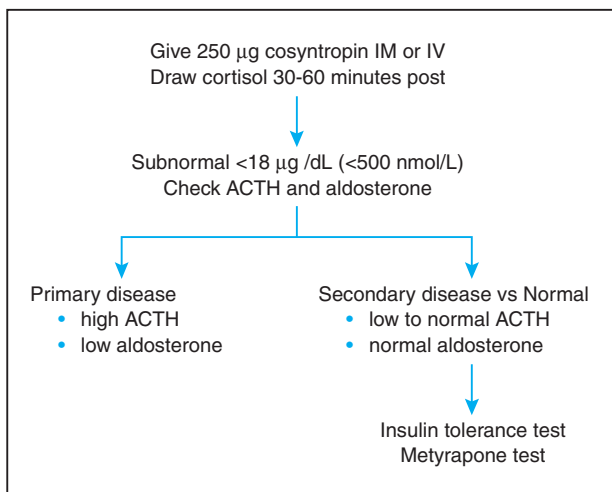
- Dysfunction at the level of the pituitary or hypothalamus
- Incidence of 150-280 per million; age at diagnosis peaks in the sixth decade of life
- Seen in patients with recurrent steroid pulses or chronic steroid use; much more common than primary insufficiency due to widespread use of exogenous steroids

Pearls of the History and Physical Examination

- Most common symptoms are nonspecific: generalized weakness, fatigue, malaise, anorexia, occasional nausea/vomiting, diarrhea, and orthostatic hypotension
- Most sensitive and specific sign for primary adrenal insufficiency is hyperpigmentation (due to elevated ACTH), especially of palmar creases, knuckles, and oral mucosa (94% of patients); hyperpigmentation is absent in secondary adrenal insufficiency
- Electrolyte disturbances common in primary adrenal insufficiency (92%), with hyponatremia and hyperkalemia being the most frequent; hyperkalemia is absent in secondary adrenal insufficiency due to intact mineralocorticoid function
- Acute adrenal insufficiency can often present in intensive care unit (ICU) patients with underlying subclinical disease, ranging from relative insufficiency to frank Addisonian crisis; patients with sepsis have increased mortality risk if adrenal insufficiency is not corrected⁴
- Adrenal crisis is uncommon; presents as rapid, dramatic clinical decline with hypotension, hemodynamic instability, fever, abdominal pain, confusion, and often neuropsychiatric manifestations

Diagnostic Studies and Laboratory Values

- Diurnal variation and wide response range of cortisol levels in patients have caused debate on preferred screening tests; method of choice is a high-dose (250 µg) cosyntropin test for screening primary adrenal insufficiency; screening for secondary adrenal insufficiency requires tests that stimulate the hypothalamus^{1,5}
- Mild disease is difficult to diagnose and may require repeat follow-up screening if clinical suspicion is high
- Basal AM cortisol drawn at 8-9 a.m. can be diagnostic in some cases^{1,6}
 - <4 µg/dL (<100 nmol/L) diagnostic
 - 18 µg/dL (500 nmol/L) or greater excludes disease
- Random cortisol in ICU or critically ill patients can be used due to loss of diurnal variation under stress.
 - <25 µg/dL (700 nmol/L) highly suggestive of adrenal insufficiency in critically ill patients⁷



High dose cosyntropin stimulation test.⁶

Guide to Acute Management

Chronic Steroid Replacement

- Hydrocortisone 15-25 mg/d two-thirds in morning and one-third in late afternoon
 - Monitor clinical response; following cortisol or ACTH levels is not useful
- Fludrocortisone 0.05-0.1 mg/d (for primary insufficiency) with measurement of plasma renin activity to assess adequacy of fludrocortisone therapy
 - Monitor blood pressure, electrolytes, sodium intake

Stress Situations in Patients Receiving Chronic Steroids^{4,7}

- Fever: double hydrocortisone dose
- Severe illness: increase dose to 75-150 mg/d
- Surgery or dental procedure: requires stress dosing

Relative Adrenal Insufficiency in Critically Ill Patients^{3,4}

- Critical illness, such as septic shock, may be associated with relative adrenal insufficiency even in patients not taking corticosteroids
- Corticosteroids often used when shock refractory and patients are vasopressor-dependant
- One study reported improved outcomes with low-dose hydrocortisone (50 mg intravenously every 6 hours) and fludrocortisone (50 µg po every day) for 7 days³ for patients with relative adrenal insufficiency (nonresponders to ACTH)

Acute Adrenal Crisis^{4,5,7}

- Draw baseline cortisol and give cosyntropin test if time and patient condition permit
- IV fluids should include D5NS (treats shock and hypoglycemia)
- Bolus 100 mg hydrocortisone and continue 50-100 mg every 6 hours

- Treat hypotension: replace salt and free water deficits
- Vasopressors as adjunctive therapy
- Can taper steroids after first 24 hours to 50 mg IV/IM every 6 hours and then switch to oral taper
- Pearl: hyperthyroidism increases cortisol clearance, so thyrotoxic patients with adrenal insufficiency will require 2-3 times more glucocorticoids; conversely, when hypothyroidism coexists with adrenal insufficiency, replace glucocorticoids adequately before starting thyroxine to avoid precipitating adrenal crisis



Patient Care Warnings

- Be aware of potential for adrenal insufficiency when giving steroid tapers to patients with history of multiple courses of steroids
- If concerned for adrenal crisis/insufficiency in a critically ill, unstable patient, draw a random cortisol and ACTH emergently and proceed to treat with corticosteroids
- Remember to give additional stress-dosed steroids to patients on chronic replacement when they are febrile or undergoing surgery

References

- ③ 1. Arlt W, Allolio, B. Adrenal insufficiency. *Lancet* 2003;361:1881-93.
- ③ 2. Mayo J, Collazos J, Martinez E, et al. Adrenal function in the human immunodeficiency virus-infected patient. *Arch Intern Med* 2002;162:1095-98.
- ① 3. Annane D, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;288:862-71.

- ③ 4. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *New Engl J Med* 2003;348:727-34.
- ③ 5. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003;139:194-204.
- ③ 6. Roux CW, Meeran K, Alaghband-Zadeh J. Is a 0900-H serum cortisol useful prior to short Synacthen test in outpatient assessment? *Ann Clin Biochem* 2002;39:148-150.
- ③ 7. Marik PE, Aloga GP. Adrenal insufficiency in the critically ill: A new look at an old problem. *Chest* 2002;122:1784-96.

INFECTIOUS DISEASE

ORGANISMS AND GRAM STAINS

GRAM-POSITIVE COCCI

Catalase-Positive: Staphylococci

Coagulase-positive:
Staphylococcus aureus
(beta hemolysis)
Coagulase-negative:
*Staphylococcus epider-
midis*, *Staphylococcus
saprophyticus*

Catalase-Negative: Streptococci

Beta-hemolytic:

- Lancefield group A (bacitracin-sensitive): *Streptococcus pyogenes*
- Lancefield group B (bacitracin-resistant): *Streptococcus agalactiae*

Alpha hemolytic:

- Lancefield group D:
 - Grows in 6.5% NaCl: *Enterococcus faecalis*
 - No growth in 6.5% NaCl: *Streptococcus bovis*
- No Lancefield group determination:
 - Bile-soluble, inhibited by optochin: *Streptococcus pneumoniae*
 - Not bile-soluble, not inhibited by optochin: *Streptococcus viridans*

GRAM-NEGATIVE COCCI

Polysaccharide Capsule

Neisseria meningitidis

No Polysaccharide Capsule

Neisseria gonorrhea

GRAM-POSITIVE RODS

Spore-forming

Bacillus: *B. anthracis*, *B. cereus*

Clostridium: *C. tetani.*, *C. botulinum*, *C. perfringens*, *C. difficile*

Nonspore-forming

Club-shaped: *Corynebacterium diphtheria*

V- or L-shaped: *Listeria monocytogenes*

GRAM-NEGATIVE RODS

Lactose
Fermenter

Escherichia coli,
Enterobacter
cloacae,
Klebsiella
pneumonia

Nonfermenter

Proteus
mirabilis,
Pseudomonas
aeruginosa,
Shigella,
Salmonella

Slow
Fermenter

Serratia,
Vibrio

Microaerophilic

Campylobacter

Grows On
Chocolate Agar

Haemophilus

Media
Supplemented with
Iron and Cysteine

Legionella

Bordet-Gengou
Medium

Bordetella

ACID-FAST ORGANISMS

Tuberculous	Nontuberculous
<i>Mycobacterium tuberculosis</i>	Photochromogens: <i>Mycobacterium kansasii</i> , <i>M. marinum</i> Scotochromogens: <i>Mycobacterium scrofulaceum</i> Nonchromogens: <i>Mycobacterium avium-intracellulare</i> complex Rapidly growing mycobacteria: <i>Mycobacterium fortuitum-chelonae</i> complex <i>Mycobacterium leprae</i>

GRAM-POSITIVE BRANCHING FILAMENTS

Sulfur Granules Present	Weakly Gram-Positive/Acid-Fast
<i>Actinomyces israelii</i>	<i>Nocardia asteroides</i> , <i>Nocardia brasiliensis</i>

OBLIGATE INTRACELLULAR ORGANISMS

No Cell Wall	Rigid Cell Wall Without Peptidoglycan Layer	Short Gram-Negative Rod
<i>Mycoplasma pneumonia</i>	<i>Chlamydia</i>	<i>Rickettsia</i>

SPIROCHETES

Darkfield Microscopy	With Giemsa Stains
<i>Treponema pallidum</i> , <i>Leptospira interrogans</i>	<i>Borrelia burgdorferi</i>

Definitions, Etiology, and Epidemiology

- Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock are the currently accepted categories for patients displaying signs of a systemic response to initial insult, whether or not the insult is infection and in patients with or without organ dysfunction¹
- Future categories may include the PIRO model (classifying patients based on *P*redisposing conditions, *I*nsult, patient *R*esponse to insult, and *O*rgan dysfunction) or biomarkers such as IL-6, procalcitonin, and C-reactive protein; there is no laboratory test that can reliably identify sepsis or provide prognostic information about the septic patient
- Most recent consensus definition on sepsis includes²:
 - Suspected or documented infection and some of the following:
 - Temperature $>38.3^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
 - Heart rate >90 bpm or more than two standard deviations above the mean for age
 - Tachypnea
 - Altered mental status
 - Positive fluid balance
 - Hyperglycemia without diabetes
 - White blood cell count >12 k or <4 k, or a normal count with 10% immature forms
 - Plasma C-reactive protein and plasma calcitonin levels more than two standard deviations above the mean
 - Systolic blood pressure (SBP) <90 mm Hg, mean arterial pressure (MAP) <70 , or an SBP decrease >40 mm Hg
 - Mixed venous oxygen saturation $<70\%$
 - Elevated serum lactate level

- Prothrombin time/partial thromboplastin time elevation
- Cardiac index >3.5 L/min/m²
- Acute oliguria or azotemia
- Hyperbilirubinemia
- Ileus
- SIRS defined as abnormalities in at least two of the following: fever or hypothermia; tachycardia; tachypnea; and leukocytosis, leucopenia, or a “left shift” in which immature neutrophils comprise 10% of the count
- Sepsis is SIRS that is believed to be caused by infection
- Severe sepsis is defined as sepsis with hypotension and organ dysfunction
- Septic shock is severe sepsis with hypotension refractory to adequate volume resuscitation with organ dysfunction
- Tenth most common cause of death in the United States³; 750,000 cases of severe sepsis occur each year, occurring more frequently in men and in non-whites; although gram-negative organisms are commonly believed as causing sepsis, gram-positive microbes are now the most common cause of sepsis

Causative Organisms ⁴	Frequency (%)
Gram-positive	30–50
Methicillin-susceptible <i>Staphylococcus aureus</i>	14–24
Methicillin-resistant <i>S. aureus</i>	5–11
<i>Streptococcus pneumoniae</i>	9–12
<i>Streptococcus</i> (other)	6–11
<i>Enterococcus</i>	3–13
Gram-negative	25–30
<i>Escherichia coli</i>	9–27
<i>Pseudomonas</i>	8–15
<i>Candida</i>	1–3

- Disseminated fungal infections are now a much more common cause of sepsis, rising more than 200% from 1979 through 2000⁵
- Risk for developing sepsis includes underlying medical condition (especially an immunocompromised state), presence of indwelling catheters and other foreign objects.
- A genetic predisposition has been defined; polymorphisms have been identified in genes encoding various immune modulators, such as tumor necrosis factors, IL-6 and 10, and toll-like receptors; as the pathophysiology of sepsis is further explained, perhaps those at greatest risk can be more aptly identified
- The pathophysiology of sepsis is complex and evolving; it involves interactions of the immune system with invading pathogens in the local tissue environment⁴

Guide to Acute Management

- Centered around early recognition and prompt resuscitation (consensus in 2003 from Surviving Sepsis Campaign)⁶

Fluid and Volume Resuscitation

- Initial goal is maintaining (initial recommendations are supported by a single center randomized trial)⁷
 - Central venous pressure (CVP) of 8–12 mm Hg (12–15 in positive pressure ventilation)
 - MAP of 65 mm Hg
 - Urine output >0.5 mL/kg/hr
 - Mixed venous oxygen saturation (MV_O₂) of greater than 70%
- Fluid choice is clinician's discretion
 - No evidence exists to support use of crystalloid versus colloid for septic patients, and studies in

surgical and other patients do not suggest superiority of one over the other

- Patients in whom hypovolemia is anticipated may be challenged with intravenous fluid boluses, with careful monitoring for complications of pulmonary edema
- Crystalloid resuscitation induces peripheral edema, and measurement of input/output ratio is not an accurate indication of restoration of arterial volume
- Transfusing packed red blood cells in critically ill patients has not been associated with decreased mortality rates; failure of the MVO_2 to correct to at least 70% with correction of the CVP warrants transfusion of packed red cells to a hematocrit level of 30% or initiation of a dobutamine infusion (maximum of 20 $\mu\text{g/kg/min}$) to elevate the MVO_2 to 70%
- No specific target hemoglobin level in the septic patient has been identified, but beyond a low oxygen tension within the initial resuscitation a hemoglobin range of 7–9 g/dL may be targeted
- Erythropoietin should not be used for sepsis-induced anemia but may be continued for other indications such as anemia of renal failure

Antibiotics

- Prompt therapy warranted, although no prospective data support this recommendation
- Before initiation of antibiotics, appropriate cultures should be obtained
 - Two blood cultures should be drawn, one from a peripheral site and one from each indwelling catheter >48 hours old; other appropriate cultures should be obtained as the clinical situation dictates
- Appropriate diagnostic imaging studies should be obtained
- If a source of infection is identified, prompt intervention should be taken to control the source

- Initiation recommended within the first hour of resuscitation; choice of antibiotics is determined by the clinical scenario, should cover the suspected organism(s), and penetrate appropriate tissues
- Due to considerable mortality from sepsis, it is reasonable to choose broad-spectrum antibiotics until culture results can help tailor therapy; a full loading dose is recommended, followed by appropriate dosing should organ impairment occur
- Typical 7-10-day course is recommended based on clinical response; no evidence exists for combined therapy, although some recommend combination therapy for *Pseudomonas* infection and for patients with neutropenic fever

Vasopressors (in Septic Shock)

- Few data guide initial vasopressor choice, but physiological data suggest dopamine and norepinephrine (through a central venous line) to be reasonable first choices
- Low-dose dopamine (with the rationale of preserving renal perfusion) has not been shown to be of benefit and should not be used in the treatment of sepsis⁸
- An arterial catheter should help monitoring of arterial blood pressure
- Vasopressin can be considered at a rate of 0.01–0.04 U/min in shock refractory to other vasopressors; higher doses are associated with cardiac dysfunction

Inotropes

- Patients with low cardiac output with adequate left ventricular filling pressures may benefit from addition of an inotrope
- Dobutamine is the first-line agent in these situations
- Elevation of cardiac index to a specific target has not been shown to be beneficial⁹

Steroids

- Hydrocortisone (200–300 mg/d for 7 days, continuous or in three to four divided doses) is recommended for hypotension refractory to adequate fluid resuscitation requiring vasopressors
- Doses >300 mg daily are ineffective and might be harmful
- Some use an adrenocorticotrophic hormone (ACTH) stimulation test (positive response to 250 µg ACTH defined as greater than 9 µg/dL increase in cortisol in 60 minutes) to identify those with relative adrenal insufficiency, but steroids should be initiated before results have returned (note that dexamethasone will not interfere with the ACTH stimulation test)
- Some suggest that a random cortisol level <15–25 µg/dL in the critically ill patient is sufficient to make a diagnosis of relative adrenal insufficiency and warrants stress-dose steroid initiation (see section titled Adrenal Insufficiency in Chapter 7)
- No role for higher-dose (>300 mg/day) steroids or steroids in the absence of shock

Recombinant Human Activated Protein C (rhAPC, Xigris)

- APC is an endogenous anticoagulant and anti-inflammatory agent
- Use is suggested in patients at high risk of death (APACHE II score at least 25, multiorgan failure, septic shock, or sepsis-induced acute respiratory distress syndrome), in patients without an absolute contraindication (mainly related to bleeding complications)¹⁰
- In the single phase III clinical trial that showed efficacy, APC was administered within 24 hours of the onset of severe sepsis
- Contraindications:¹¹
 - Active internal bleeding

- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

Other

- Ventilation: see the sections titled Mechanical Ventilation and Acute Respiratory Distress Syndrome in Chapter 2
- Tight glycemic control has not been shown to be beneficial prospectively in septic patients, but a goal glucose <150 mg/dL is beneficial in postoperative patients¹² and in a post hoc analysis of septic patients¹³
 - Can best be achieved by a continuous glucose-insulin infusion
 - Nutrition should be maintained preferably by the enteral route
- Acute renal failure: see the section titled Overview and Indications for Renal Replacement Therapy in Chapter 4
- Bicarbonate therapy has not been shown to be beneficial and is not recommended for pH >7.15 ¹⁴
- Deep vein thrombosis (DVT) prophylaxis should be provided, with subcutaneous unfractionated or low molecular weight heparin, unless a contraindication exists
 - Sequential compression devices or other mechanical prophylactic devices should be used in patients without peripheral vascular disease; the combination of the two may be used in high-risk patients
- Stress ulcer prophylaxis with H₂ receptor blockers; proton pump inhibitors have not been evaluated



Patient Care Warnings

- Do not overlook DVT and stress ulcer prophylaxis
- Intervene early with appropriate or empiric antibiotics

References

1. Carson S, Shorr AF. Is the implementation of research findings in the critically ill hampered by the lack of universal definitions of illness? *Crit Care Outcomes* 2003;9:308-15.
- 1 2. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference *Crit Care Med* 2003;31:1250-56.
- 1 3. Annane D, Bellissant E, Cavaillon J. Seminar: Septic shock. *Lancet* 2005;365:63-78.
- 1 4. Riedemann NC, Guo R, Ward P. The enigma of sepsis. *J Clin Invest* 2003;112:460-67.
- 2 5. C Alberti, C Brun-Buisson, H Burchardi, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002;28:108-21.
- 3 6. Dellinger RP, Carlet JM, Maaub H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858-73.
- 1 7. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
- 1 8. Kellum J, Decker J. Use of dopamine in acute renal failure: A meta-analysis. *Crit Care Med* 2001;29:1521-31.
- 1 9. Gattitoni L, Brazzi L, Relosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med* 1995;353:1025-32.
- 1 10. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;344:699-709.
- 3 11. <http://www.xigris.com/about/safety.jsp>
- 1 12. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345:1359-67.
- 2 13. Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. *JAMA* 2003;20:41-47.
- 1 14. Cooper DJ, Wally KR, Wiggs BR, et al. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis: A prospective, controlled clinical study. *Ann Intern Med* 1990;112:492-98.

NEUTROPENIC FEVER

Definitions, Etiology, and Epidemiology

- Neutropenia: absolute neutrophil count (ANC) ≤ 500 , or ANC ≤ 1000 with predicted nadir ≤ 500
 - ANC: white blood cell $\times$ (% neutrophils + % bands); immature progenitors other than bands (e.g., metamyelocytes) not counted
- Neutropenic fever: neutropenia + temperature $\geq 38.3^{\circ}\text{C}$ (101.3°F), or sustained temperature of 38.0°C (100.4°F) for more than 1 hour
- Certain factors (e.g., overwhelming sepsis, advanced age, corticosteroid use) may mask fever in the setting of neutropenia; thus, neutropenic patients with hypothermia and/or declining clinical status should be considered for treatment despite the absence of true fever
- Risk factors
 - Degree of neutropenia (highest morbidity/mortality rate with ANC <100)¹
 - Rapid rate of ANC decline
 - Hematological malignancies (poor neutrophil function)
 - Prolonged neutropenia (>7 days)
 - Induction chemotherapy
 - Poor nutritional status
 - Medical comorbidities or widely disseminated malignancy
 - Hospitalization
 - Lymphatic, biliary, urinary, or gastrointestinal obstruction
 - Comorbid immunocompromised states (myeloma, HIV, asplenia, chronic lymphocytic leukemia, high-dose corticosteroids)
 - Loss of mucosal or cutaneous integrity (mucositis, intravascular access, tumor invasion, postoperative state)

Pearls of the History and Physical Examination

History

- Comorbid medical conditions (e.g., HIV, asplenia)
- Sick contacts
- Recent antibiotic administration
- Presence of central access catheters (e.g., peripherally inserted central catheter lines, tunneled catheters, or subcutaneous ports)
- Detailed drug allergy and hypersensitivity history
- Prolonged corticosteroid use (increased incidence of *Pneumocystis carinii* and may indicate need for stress doses if patient adrenally suppressed)
- Focal symptoms may be subtle or absent due to impaired inflammatory response

Physical Examination

- Classic stigmata of infection (e.g., pus) may be subtle or absent
- Even mild erythema at insertion sites of indwelling catheters may be significant
- Examine oropharynx and perianal area for ulcers or abscesses (herpes, fungi, mycobacteria)
- Examine skin for clues, e.g., fungal skin lesions, ecthyma gangrenosum, etc.
- Although endocarditis quite rare, consider in the differential
- Avoid digital rectal examinations or rectal temperatures if possible
- Physical examination should be reassessed daily, particularly as ANC rebounds

Diagnostic Studies and Laboratory Values

- Blood tests: baseline complete blood count with differential
- Two or three sets of *peripherally* obtained blood cultures

- Chest x-ray: consider repeating if fever persists and counts begin to rise
- Urinalysis, culture, and sensitivities (pyuria or leukocyte esterase may be attenuated or absent)
- Lumbar puncture *only* if localizing signs and symptoms are present (pleocytosis may be attenuated or absent)
- If pulmonary symptoms or infiltrate, sputum culture should be attempted, but sputum production is often scant; consider acid-fast bacilli stain or direct fluorescent antibody for *Pneumocystis* (especially if patient received fludarabine) if history is suggestive
- Repeat blood cultures in the setting of new rigors or persistent fevers; cultures may be performed daily or upon onset of clinical deterioration or change
- If clinically indicated: computed tomography imaging of the brain, sinuses, chest, abdomen, or pelvis; skin or ulcer biopsies; endoscopic visualization and biopsy of esophagus (especially for herpes simplex virus [HSV]), stool studies (especially for *Clostridium difficile*)
- Line cultures are controversial
 - A positive line culture does not necessarily define the source of bacteremia (if the line is positive for the same pathogen as from peripheral blood, it is usually the source)
 - Colonization is common in long-term indwelling catheters, particularly in the case of coagulase-negative staphylococci; this is particularly true in neutropenic febrile patients, who are often infected with gram-negative enteric pathogens, frequently without yield from routine culture methods; conversely, a positive peripherally drawn culture (particularly for *Staphylococcus aureus* or *Candida*) in the setting of a negative line culture probably necessitates removal of the catheter^{2,3}
- In patients with neutropenic fever with semipermanent access for the administration of chemotherapy

or blood products, attempts to “treat through” infections are made in an effort to avoid surgical removal and replacement of these catheters; few data exist to support or refute this practice

Guide to Acute Management

- Median time to defervescence is 5 days⁴
- Always cover for *Pseudomonas* (cefepime, ceftazidime, carbapenems, antipseudomonal penicillins, ciprofloxacin, aminoglycosides)⁵
- Dual therapy and monotherapy have equivalent efficacy^{6,7} (dual therapy may decrease emergence of resistance⁸)
- Consider previous antibiotic exposure history when choosing a regimen
- Select bactericidal agent(s) whenever possible
- Be familiar with institutional and/or community resistance patterns; if high rate of extended-spectrum beta lactamase, use carbapenems (avoid cephalosporins)
- If *S. aureus* infection or candidemia identified, pre-existing indwelling catheters *must* be removed

Guidelines (Adapted From 2002 Infectious Diseases Society of America Executive Summary)⁹

- Initial antibiotic therapy
 - Monotherapy:
 - Cefepime or ceftazidime
 - Imipenem or meropenem
 - Dual therapy
 - Aminoglycoside + antipseudomonal beta-lactam *or*
 - Carbapenem
 - Add vancomycin only if serious catheter-related infection suspected (based on appearance), patient is hypotensive, preliminary blood cultures have gram-positive cocci, patient known to be colonized with methicillin-resistant *S. aureus*, or

has history of recent quinolone prophylaxis or severe mucositis

- Oral therapy (if low risk and very close follow-up): ciprofloxacin + amoxicillin-clavulanate
 - *Low risk*: ANC >100, monocytes >100, normal chest x-ray, no evidence of catheter-related infection, temperature <39°C, no serious comorbidities, normal liver and renal function, absent abdominal pain, and neutropenia expected to persist <10 days
- First 3 days of treatment (afebrile)
 - Etiology identified: base treatment on culture results or known antimicrobial spectra
 - Etiology unknown:
 - Low risk: change to oral therapy (see above) after 48 hours
 - High risk: continue intravenous (IV) antibiotics
- First 3 days of treatment (febrile)
 - Clinically unchanged: continue same antibiotic regimen; stop vancomycin if cultures are negative
 - Progressive disease: change to alternative initial antibiotic regimen (see above)
- Day 5 (febrile)
 - Add antifungal therapy to existing regimen if no source of infection is found as morbidity and mortality rates associated with fungal infections (mostly *Aspergillus* species) are high and diagnosis is often delayed
 - Commonly: *amphotericin B* or *liposomal amphotericin B*
 - However, a study of 384 patients found statistically equivalent efficacy between liposomal amphotericin B and IV itraconazole, with significantly fewer adverse events in the latter group (5% vs. 54%); itraconazole is contraindicated for patients with creatinine clearance <30 mL/min; should not be used for more than 14 days and is ineffective against *Aspergillus*¹⁰
 - Voriconazole is a newer agent with activity against *Aspergillus* and less nephrotoxicity than amphotericin

B; a study found it to be nearly as effective as amphotericin B in achieving defervescence in febrile neutropenia (26% vs. 30.6%, respectively), with no difference in mortality rate¹¹

- Therapy duration
 - Afebrile at day 3
 - ANC >500 for 48 hours: stop antibiotics if no evidence of infection and cultures negative
 - ANC <500 at day 7
 - Low risk (see above): stop antibiotics when afebrile for 5-7 days
 - High risk: continue antibiotics
 - Persistent fever
 - ANC <500: continue antibiotics for 2 more weeks, then reassess
 - ANC >500: stop antibiotics after ANC >500 for 4-5 days and reassess
- Other therapies
 - Antiviral therapy: only if HSV/varicella-zoster virus/cytomegalovirus evident clinically
 - Granulocyte infusions: not routine at present
 - Colony-stimulating factors: not routine at present
 - Studies of colony-stimulating factors have shown a small decrease in duration of neutropenia, fever, and hospitalization but no decrease in mortality rate; at present, they are recommended only in the setting of critical illness (hypotension, organ dysfunction, pneumonia) or when recovery of marrow is anticipated to be unusually protracted¹²



Patient Care Warnings

- Always cover for *Pseudomonas*, and consider antifungal therapy appropriately as mortality rate is high

References

- ③ 1. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med* 1993; 328:1323.
- ③ 2. Fatkenheuer G, et al. Central venous catheter (CVC)-related infections in neutropenic patients: Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol* 2003;82 (Suppl 2):S149-57.
- ③ 3. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001;32:1249-72.
- ① 4. Maher DW, Lieschke GJ, Green M, et al. Filgrastim in patients with chemotherapy-induced febrile neutropenia: A double-blind, placebo-controlled trial. *Ann Intern Med* 1994;121:492-501.
- ② 5. Rolston KV, Tarrand JJ. *Pseudomonas aeruginosa*—still a frequent pathogen in patients with cancer: 11-Year experience at a comprehensive cancer center. *Clin Infect Dis* 1999;29:463-64.
- ① 6. Leyland MJ, Bayston KF, Cohen J, et al. A comparative study of imipenem versus piperacillin plus gentamicin in the initial management of febrile neutropenic patients with haematological malignancies. *J Antimicrob Chemother* 1992;30:843.
- ① 7. Pizzo PA, Hathorn JW, Hiemenz J, et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med* 1986;315:552.
- ② 8. Johnson MP, Ramphal R. Beta-lactam-resistant *Enterobacter* bacteremia in febrile neutropenic patients receiving monotherapy. *J Infect Dis* 1990;162:981.
- ③ 9. Hughes WT, Armstrong D, Bodey GP, et al. 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730.
- ① 10. Boogaerts M, Winston DJ, Bow EJ, et al. Intravenous and oral itraconazole versus intravenous amphotericin B deoxycholate as empirical antifungal therapy for persistent fever in neutropenic patients with cancer who are receiving broad-spectrum antibacterial therapy: A randomized, controlled trial. *Ann Intern Med* 2001;135:412.
- ① 11. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med* 2002;346:225.
- ③ 12. Ozer H, Armitage JO, Bennett CL, et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. *J Clin Oncol* 2000;18:3558-85.

CRITICAL CARE OF THE PATIENT WITH HIV

Definitions, Etiology, and Epidemiology

- Highly active antiretroviral therapy (HAART) has significantly affected the spectrum of inpatient HIV demographics and management in developed countries where patients have access to standard of care
- Morbidity rate remains high in U.S. populations with limited access to care, poor adherence, and/or comorbidities (e.g., end-stage liver disease)¹
- In the HAART era (post-1996), HIV has increasingly become a comorbid condition rather than an admitting or contributing diagnosis
- HAART has brought a new constellation of clinical complications, such as the immune reconstitution syndrome, metabolic and cardiovascular disease, atypical presentations of infections, drug interactions, and drug toxicities
- Consultation with a specialist in HIV management should be considered in the treatment of the HIV-positive intensive care unit (ICU) patient
- In a study of ICU admissions between 1996 and 1999 at San Francisco General Hospital, 63% of patients were admitted with a non-AIDS associated condition²; in 2003, most common ICU admitting diagnoses included respiratory failure (40%-50%), central nervous system (CNS) disease (11%-27%), sepsis (10%-15%), gastrointestinal bleeding (6%-15%), and cardiovascular disease (8%-13%)³
- Myocardial infarction and drug overdose are increasingly significant causes for ICU admission due to emergence of metabolic disease and changes in patient demographics, respectively
- Average length of stay is approximately 5-11 days, with a mortality rate of 30%-40% (decreased from 70% in the early 1980s)³

Predictors of Increased Mortality³

- Sepsis
- Respiratory failure (particularly *Pneumocystis carinii* pneumonia [PCP])
- Decreased serum albumin
- History of weight loss
- Advanced age and comorbid disease
- Disease severity scores (APACHE II, SAPS I)
- CD4+ counts and plasma HIV RNA level have not been shown to predict mortality during short-term ICU admissions

Respiratory Disease

- PCP is the most common cause of respiratory failure, but recent data indicate a decline in incidence
- Bacterial pneumonia is the second most common cause of respiratory failure (*Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Staphylococcus aureus*)
- Other: *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Aspergillus fumigatus*, cytomegalovirus (CMV) (rare), Kaposi's sarcoma (KS), *Toxoplasma gondii*, non-Hodgkin's lymphoma, lymphocytic interstitial pneumonia, chemical (crack) pneumonitis, and drug overdose
- At Parkland Memorial Hospital in 1991, 27% of spontaneous pneumothoraces occurred in HIV patients (due primarily to rupture of PCP-induced subpleural cysts)⁴

GI Disease

- CMV enteritis/peritonitis is the most common life-threatening cause of abdominal pain in HIV; frank evidence of perforation may be absent
- Etiologies of upper GI disease include infectious esophagitis (CMV or herpes simplex virus [HSV]),

KS, lymphoma, AIDS cholangiopathy (multiple etiologies), and peptic ulcer disease

- Etiologies of lower GI disease include CMV colitis, idiopathic colonic ulcers, KS, lymphoma, and *Mycobacterium avium* complex
- Bleeding is more common in the upper than in the lower GI tract in HIV patients
- Concomitant viral hepatitis B or C may result in significant comorbidity (varices)

CNS Disease

- Aseptic meningitis and Guillain-Barré syndrome can occur at any CD4+ count
- Causes of serious CNS disease in late-stage HIV include cryptococcal meningitis, HSV and CMV encephalitis, CNS toxoplasmosis, primary CNS lymphoma, progressive multifocal leukoencephalopathy, syphilis, and tuberculous meningitis
- Incidence of stroke or intracerebral hemorrhage has been increasing, possibly secondary to increased metabolic disease and/or sympathomimetic abuse
- Immune reconstitution (initiation of antiretroviral therapy) may precipitate severe disease flares in patients with latent or subacute opportunistic infections (most commonly *Mycobacterium tuberculosis* and cryptococcus)

Adrenal Disease

- Decreased adrenal reserve is present in 8%-14% of AIDS patients^{5,6}
- Baseline cortisol measurements may be normal or elevated, but response to stress or adrenocorticotrophic hormone provocation may be significantly blunted
- Some patients also exhibit evidence of peripheral cortisol resistance
- All patients with AIDS should be considered at risk for adrenal insufficiency

Pearls of the History and Physical Examination

History

- Do not restrict focus of history based on the presumption of an HIV-related diagnosis
- Comprehensive medication history, including over-the-counter and herbal preparations; be aware of drug interactions and medication side effects
- Carefully review HAART history, with particular attention to present regimen
 - Abacavir: potentially fatal hypersensitivity reaction with multiorgan dysfunction
 - Zidovudine + corticosteroids: severe myopathy and respiratory muscle dysfunction
 - Zidovudine: severe anemia
 - Nucleoside analogs: potentially severe lactic acidosis/hepatic steatosis
 - DDI, D4T, pentamidine: pancreatitis
 - Tenofovir: Fanconi's syndrome, renal failure
 - Nevirapine: fulminant hepatitis (particularly in women), Stevens-Johnson syndrome/toxic epidermal necrolysis
 - Enfuvirtide (T20): potential increased risk of bacterial pneumonia
 - Protease inhibitor-containing regimen: hyperlipidemia, metabolic syndrome, diabetic ketoacidosis, coronary artery disease
 - Recent initiation of therapy: immune reconstitution syndrome with acute exacerbation of underlying opportunistic infections (cryptococcosis, tuberculosis, systemic atypical mycobacterial disease, PCP)
- Previous opportunistic infections (OIs) and subsequent OI prophylaxis
- History of multidrug-resistant pathogens
- Injection drug use
- If possible, investigate any advance directives or surrogate designations (not always next of kin)

Physical Examination

- The absence of physical stigmata of lipodystrophy (peripheral/facial lipoatrophy, central obesity, buffalo hump) does *not* predict the absence of metabolic disease (hyperlipidemia, insulin resistance)
- In a patient with respiratory compromise, always listen for decreased or absent breath sounds indicating possible PCP-associated pneumothoraces
- 50% of patients with PCP have an unremarkable lung examination
- >80% of patients with PCP have fever $>38.1^{\circ}\text{C}$ ⁷

Diagnostic Studies and Laboratory Values

- PCP (see section titled PCP and Other HIV-Related Pulmonary Diseases)
- Histoplasmosis (see section titled PCP and Other HIV-Related Pulmonary Diseases)

Gastrointestinal CMV

- Diagnosis is usually made by the presence of physical symptoms (abdominal pain, odynophagia, diarrhea), visualization on endoscopy of GI ulcers, and histological evidence of CMV-associated tissue pathology
- Viral cultures of GI biopsies are neither sensitive nor specific for active GI CMV disease, so histopathological confirmation showing intranuclear inclusions is essential

Tuberculous Meningitis

- Cerebrospinal fluid (CSF) studies typically reveal elevated protein, low glucose, and lymphocytosis
- CSF acid-fast bacilli staining is notoriously insensitive

- The utility of *Mycobacterium tuberculosis* polymerase chain reaction (PCR) is not clear, and a negative test does not exclude disease
- Purified protein derivative testing is often negative in tuberculous meningitis
- The gold standard is mycobacterial culture, but as results take weeks empiric treatment is often necessary

CNS Toxoplasmosis

- CSF studies reveal an elevated protein and a mild monocytic pleocytosis
- A positive *Toxoplasma gondii* IgG titer of the serum, combined with a CD4⁺ count <100 cells/mm³, multiple ring-enhancing lesions on computed tomography or magnetic resonance imaging, and no recent prophylaxis, is highly suggestive of CNS toxoplasmosis⁸

Cryptococcal Meningitis

- Serum cryptococcal antigen has a very high negative predictive value and equivalent sensitivity to CSF analysis⁹
- It is important to measure the opening pressure when performing a lumbar puncture on a patient with AIDS, as CSF removal and decompression may be therapeutically indicated

Primary CNS Lymphoma

- Epstein-Barr virus PCR testing of the CSF has an 80%-90% sensitivity and near 95%-100% specificity for primary CNS lymphoma¹⁰
- PET or SPECT thallium-201 imaging may be helpful for diagnosis when used with clinical/radiographic criteria and PCR¹¹

Neurosyphilis

- Neurosyphilis can occur at any stage in patients with HIV
- Serum Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) is negative in 25% of neurosyphilis cases¹²
- CSF VDRL is highly specific but insensitive
- CSF fluorescent treponemal antibody absorption test is highly sensitive but not specific and unavailable at many laboratories
- CSF leukocyte count is usually elevated (>5 cells/mm³)
- There is no definitive diagnostic standard; diagnosis is usually made on high clinical suspicion in conjunction with various treponemal and nontreponemal tests
- A positive serum nontreponemal test (RPR or VDRL) in conjunction with abnormal CSF in the absence of another explanation is sufficient evidence to treat presumptively for neurosyphilis

Guide to Acute Management

PCP (see section titled PCP and Other HIV-Related Pulmonary Diseases)

- Antiretroviral therapy should not be instituted until the completion of PCP therapy, although patients presently on ART should not interrupt it
- PCP-associated pneumothoraces rarely respond to thoracostomy alone, and surgical consultation should always be sought due to the high morbidity and complication rates associated with this condition
- Trials of noninvasive positive pressure ventilation have been shown to decrease the need for intubation and the risk of pneumothorax in at least one prospective study¹³

Bacterial Pneumonia

- Patients with AIDS admitted to the ICU with bacterial pneumonia should be covered empirically for *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* in the event of recent previous hospitalization or high community prevalence

Histoplasmosis (see section titled PCP and Other HIV-Related Pulmonary Diseases)

- Itraconazole effective in 85% of cases, but patients ill enough to require ICU admission should be initiated on intravenous amphotericin B 0.7-1.0 mg/kg/d
- Liposomal amphotericin 3-5 mg/kg IV every day is preferable for patients with renal insufficiency and may improve survival more so than nonliposomal amphotericin B¹⁴
- Patients can be switched to oral itraconazole after documented improvement (usually several days)
 - Loading dose of 200 mg po tid for 3 days, followed by maintenance dosing of 200 mg po qd or bid, depending on measured serum concentrations at week 2 of therapy
 - Caution when coadministered with agents that induce (rifampin, rifabutin, phenytoin) or inhibit (ritonavir, erythromycin) hepatic enzyme P450 CYP 3A4
- Posaconazole is a viable option for patients who fail conventional treatment
- Histoplasma-associated pericarditis does not require antifungal treatment; corticosteroids are reserved for patients with hemodynamically significant disease

CMV Colitis

- Side effects of recommended agents
 - Ganciclovir: neutropenia, thrombocytopenia
 - Foscarnet: acute tubular necrosis, hypocalcemia, transient hypomagnesemia

- Cidofovir: irreversible nephrotoxicity, Fanconi's syndrome
 - Urine protein and serum creatinine should be assessed before every dose
 - Saline hydration and probenecid decrease toxicity, although AZT should not be administered concomitantly with probenecid due to increased risk of skin reactions

AIDS Cholangiopathy

- Mainstay is fluid resuscitation and broad-spectrum antibiotics active against gram-negative enteric pathogens
- Endoscopic retrograde cholangiopancreatography with sphincterotomy may benefit septic patients with evidence of common bile duct dilation¹⁵

Cryptococcal Meningitis

- Induction therapy is IV amphotericin B (liposomal if renal insufficiency is present), 0.7 mg/kg daily, and oral flucytosine 100 mg/kg/d in four divided doses (dose adjusted for renal insufficiency) for 10-14 days
- If large volume CSF removal is required, aim for closing pressure of 10-20 cm H₂O
- If clinical improvement is observed during induction, fluconazole (400 mg/d with normal renal function) can be substituted for amphotericin and flucytosine and should be continued as consolidation therapy for 2 months
- Maintenance therapy is fluconazole 200 mg po qd indefinitely

CNS Toxoplasmosis

- Standard therapy: pyrimethamine 200 mg po loading dose, followed by 75 mg/d plus sulfadiazine 6-8 g/d po in four divided doses
- If sulfadiazine-intolerant, use pyrimethamine 200 mg

po loading dose followed by 75 mg/d plus clindamycin 600-1200 mg IV or 450 mg po qid

- Former regimen has a higher incidence of cutaneous hypersensitivity reactions but a potentially lower rate of relapse
- Pyrimethamine should be administered with folinic acid 10-25 mg/d po to prevent marrow toxicity
- Adjunctive corticosteroids should be administered only with evidence of significant mass effect



Patient Care Warnings

- G6PD deficiency should be excluded at baseline in case dapsone or primaquine therapy is required

References

- ② 1. Jain MK, Skiest DJ, Cloud JW, et al. Changes in mortality related to human immunodeficiency virus infection: Comparative analysis of inpatient deaths in 1995 and in 1999-2000. *Clin Infect Dis* 2003;36:1030-38.
- ② 2. Morris A, Creasman J, Turner J, et al. Intensive care of human immunodeficiency virus-infected patients during the era of highly active antiretroviral therapy. *Am J Respir Crit Care Med* 2002;166:262-67.
- ③ 3. Crothers K, Huang L. Critical care of patients with HIV. HIV InSite Knowledge Base 2003 at <http://hivinsite.ucsf.edu/InSite?page=kb-03&doc=kb-03-03-01>
- ② 4. Wait MA, Estrera A. Changing clinical spectrum of spontaneous pneumothorax. *Am J Surg* 1992;164:528.
- ② 5. Dobs AS, Dempsey MA, Ladenson PW, et al. Endocrine disorders in men infected with human immunodeficiency virus. *Am J Med* 1988;84:611.
- ② 6. Membreno L, Irony I, Dere W, et al. Adrenocortical function in acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1987;65:482.
- ② 7. Kales CP, Murren JR, Torres RA, et al. Early predictors of in-hospital mortality for *Pneumocystis carinii* pneumonia in acquired immunodeficiency syndrome. *Arch Intern Med* 1987;147:1413.
- ③ 8. Skiest DJ. Focal neurologic disease in patients with acquired immunodeficiency syndrome. *Clin Infect Dis* 2002;34:103-15.

- ② 9. Asawavichienjinda T, Sitthi-Amorn C, Tanyanont V. Serum cryptococcal antigen: Diagnostic value in the diagnosis of AIDS-related cryptococcal meningitis. *J Med Assoc Thai* 1999;82:65.
- ① 10. Cingolani A, De Luca A, Larocca LM, et al. Minimally invasive diagnosis of acquired immunodeficiency syndrome-related primary central nervous system lymphoma. *J Natl Cancer Inst* 1998;90:364.
- ② 11. Naddaf SY, Akisik MF, Aziz M, et al. Comparison between 201Tl-chloride and 99Tc(m)-sestamibi SPECT brain imaging for differentiating intracranial lymphoma from non-malignant lesions in AIDS patients. *Nucl Med Commun* 1998;19:47.
- ② 12. Johnson PD, Graves SR, Stewart L, et al. Specific syphilis serological tests may become negative in HIV infection. *AIDS* 1991;5:419.
- ① 13. Confalonieri M, Calderini E, Terraciano S, et al. Noninvasive ventilation for treating acute respiratory failure in AIDS patients with *Pneumocystis carinii* pneumonia. *Intensive Care Med* 2002;28:1233-38.
- ① 14. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med* 2002;137:105.
- ③ 15. Wilcox CM. Serious gastrointestinal disorders associated with human immunodeficiency virus infection. *Crit Care Clin* 1993;9:73-88.

MENINGITIS

Definition, Etiology, and Epidemiology

- Purulent/fulminant: bacterial meningitis with acute onset (hours to days)
- Chronic: meningitis with subacute onset (weeks to months) caused by various organisms (*Mycobacterium tuberculosis*, fungi, spirochetes)
- Aseptic: viral meningitis, usually self-limited; most commonly enteroviruses (>50% of cases), herpes simplex virus, HIV, lymphocytic choriomeningitis, mumps, spirochetes, medications (Bactrim, penicillin, nonsteroidal anti-inflammatory drugs, INH), autoimmune (systemic lupus erythematosus, sarcoid, rheumatoid arthritis), or neoplasms

Age Range	Most Common Pathogens ¹
Neonates	Group B streptococcus, <i>Listeria monocytogenes</i> , <i>Escherichia coli</i> , gram-negative bacilli, enterococci
1–23 months	<i>Staphylococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , group B streptococcus
2–18 years	<i>N. meningitidis</i> , <i>S. pneumoniae</i> (decreasing number of <i>Haemophilus influenzae</i> in children age 2–5 years), enteroviruses
18–60 years	<i>S. pneumoniae</i> , <i>N. meningitidis</i>
Older than 60 years	<i>S. pneumoniae</i> , <i>Listeria monocytogenes</i> , <i>N. meningitidis</i> , gram-negative bacilli

- Mortality rate is 19%-25% with a 50% complication rate (age >60 years, hypotension, altered mental status, seizures within the first 24 hours = worse outcomes); higher mortality rate in those with advanced liver disease, HIV, and organ transplant²
- Predisposing factors include cribiform plate fracture, systemic bacteremia, asplenia, HIV infection, complement deficiencies, alcoholism, central nervous system (CNS) shunts, prior neurosurgery, and steroid use

Organism	Risk Factors/Clues
<i>S. pneumoniae</i>	Asplenia, CNS trauma with cerebrospinal fluid (CSF) leak, alcoholism, hypogammaglobulinemia, multiple myeloma, HIV, Hodgkin's disease, systemic bacteremia, i.e., Osler's triad: meningitis, pneumonia, endocarditis; usually fulminant (symptoms over hours)
<i>L. monocytogenes</i>	Alcoholics, elderly or neonates, immunosuppressed patients, patients with malignancy, iron overload; raw milk, cheese, raw vegetable ingestion, delicatessen sliced meats
<i>N. meningitidis</i>	Complement deficiency, purpuric/petechial skin rash; usually fulminant
<i>H. influenzae</i>	Asplenia, hypogammaglobulinemia, HIV, mastoiditis, recent CNS trauma or neurosurgery, CNS shunt

Organism	Risk Factors/Clues
Staphylococcus	CNS shunt, recent CNS trauma or neurosurgery
Gram-negative bacilli	Recent/current hospitalization; elderly, immunosuppressed patients; recent neurosurgery; bacteremia secondary to urinary tract infection, <i>Strongyloides</i> hyperinfection syndrome; one-third of nosocomial cases ²
Enteroviruses (coxsackievirus, echovirus, poliovirus)	Agammaglobulinemia
Herpes simplex meningitis (HSV-2)	Genital lesions present in 85% of cases (usually precede meningitis by 1 week), large percentage of Mollaret's meningitis (monocytic predominance) ³
Lymphocytic choriomeningitis	Winter; some patients may develop orchitis, parotitis, myopericarditis, arthritis; rodent urine/feces exposure
Mumps	Adolescents and unvaccinated adults, 40% without parotitis

Pearls of the History and Physical Examination

History²

Symptoms	Percentage
Fever, nuchal rigidity, and altered mental status	66%
Fever (Note: elderly may not manifest with fever); some patients have hypothermia	95%
Nuchal rigidity	88%
Abnormal mental status (confusion, delirium, lethargy, decreased consciousness)	78%
Seizures	23%
Focal neurological symptoms	28%
Photophobia	
Petechial/purpuric rash	
Headache (generalized, severe)	

Physical Examination²

- Nuchal rigidity with passive/active neck flexion
- Kernig's sign: patient supine, flex hip 90 degrees; patient will not allow full extension of knees (positive in 50% of patients)
- Brudzinski's sign: patient supine, passive flexion of neck leads to spontaneous flexion of hips (positive in 50% of patients)
- Palpable purpura or petechiae
- Papilledema (high intracranial pressure)
- Focal neurological deficits
- Jolt accentuation of headache: horizontal rotation of head 2–3 times/sec accentuates headache

Diagnostic Studies and Laboratory Values

Blood Tests

- Leukocytosis with left shift
- Disseminated Intravascular Coagulation: may be present with thrombocytopenia, elevated D-dimer, low fibrinogen, elevated prothrombin time/partial prothrombin time
- Hyponatremia if coexisting syndrome of inappropriate antidiuretic hormone secretion
- Blood cultures: positive in 50% of patients with bacterial meningitis

Lumbar Puncture

- Check opening pressure – normal <20 cm H₂O
- Studies to send:
 - Tube 1: cell count with differential
 - Tube 2: total protein, glucose
 - Tube 3: culture and Gram's stain
 - Tube 4: cell count with differential
 - Consider cytology, cryptococcal antigen, VDRL, toxoplasma antibody, fungal/viral cultures, herpes simplex virus polymerase chain reaction (PCR), MTb PCR

Diagnosis	Glucose	Total Protein	WBC (/mm ³)	Opening Pressure	Miscellaneous
Normal	45–85 mg/dL (50%–70% serum glucose)	15–45 mg/dL (50% serum total protein)	0–5 (mostly PMNs); traumatic tap, allow 1 WBC/1000 red blood cells	70–180 mm H ₂ O	
Bacterial	<45	>45 (100–1000)	>100 (100–10,000), 80% PMNs; rarely (with the exception of <i>Listeria</i>) may be lymphocytic early	Elevated	Gram's stain positive in 60%, culture positive in 73% ²
Aseptic	Normal	>45 (50–100)	10–100 (mostly lymphocytes, but PMNs may also be seen)	Normal	Herpes simplex PCR >95% sensitivity, enterovirus PCR 97% sensitivity and 100% specificity; viral cultures are infrequently positive; serum/CSF antibody for West Nile virus
TB	<45	>45 (100–500)	100–400 (mostly lymphocytes)	Elevated	Acid-fast bacillus smear positive <33% (rare), culture positive 50%–70%
Fungal	<45	>45 (50–300)	10–200 (lymphocytes)	Elevated	

- >99% predictive value for bacterial meningitis if a patient has any of the following on CSF analysis³
 - Glucose <34 mg/dL
 - CSF/serum glucose <0.23
 - Protein >220 mg/dL
 - White blood cell (WBC) count >2000/mm³
 - Polymorphonuclear (PMN) cells >1180/mm³

Guide to Acute Management

- Early initiation of treatment leads to better outcomes
- Even after initiation of antibiotics, 38% of patients may still have positive CSF cultures
- Antibiotics with bactericidal properties that can cross the blood-brain barrier are preferred
- Once Gram's stain or culture results are positive, tailor therapy to treat the causative organism
- Adjunctive corticosteroids (Solumedrol 0.15 mg/kg q 6 h × 4 days) are indicated in adults with suspected pneumococcal meningitis, positive CSF Gram's stain,

Age Range/ Risk Factors	Antibiotics
18–50 years old	Cefotaxime 2 g IV q 4–6 h or ceftriaxone 2 g IV q 12 h plus vancomycin 1 g IV q 12h (in areas where cephalosporin-resistant <i>S. pneumoniae</i> , MIC >0.5 µg/mL) ⁴
>50 years old	Cefotaxime or ceftriaxone plus vancomycin (if resistant <i>S. pneumoniae</i>) plus ampicillin 2 g IV q 4 h (for <i>Listeria</i>) +/- gentamycin for synergy
Immunocompromised	Ampicillin plus ceftazidime (50–100 mg/kg q 8 h; maximum 2 g IV q 8 h) or cefepime (1–2 g IV q 12 h) plus vancomycin (if resistant <i>S. pneumoniae</i>)
After surgery, trauma, CNS shunt	Vancomycin (to cover coagulation-negative staphylococci and <i>S. aureus</i>) plus ceftazidime (to cover <i>Pseudomonas</i> , <i>Acinetobacter</i>); imipenem (can cause seizures) or meropenem (in children and adolescents) for resistant gram-negative rods ⁵

and high risk index (hypotension, seizures, or altered mental status) at time of presentation⁶; not enough evidence to recommend for other organisms



Patient Care Warnings

- Head computed tomography (CT) prior to lumbar puncture in patients with papilledema, focal neurological deficits, seizure activity, age >60 years, immunocompromised states, abnormal level of consciousness, risk factors for HIV, and head trauma within the previous 72 hours⁷
- If awaiting head CT, draw blood cultures and start empiric antibiotics
- Always consider cryptococcal meningitis in patients with advanced liver disease (not just HIV)

References

- ② 1. Schuchat A, et al. Bacterial meningitis in the United States in 1995. *New Engl J Med* 1997;337:970.
- ② 2. Durand M, et al. Acute bacterial meningitis in adults: A review of 493 episodes. *New Engl J Med* 1993;328:21-28.
- ② 3. Spanos A, et al. Differential diagnosis of acute meningitis: An analysis of the predictive value of initial observations. *JAMA* 1989;262:2700-707.
- ③ 4. Tan TQ, et al. Antibiotic therapy and acute outcome of meningitis due to *Streptococcus pneumoniae* considered immediately susceptible to broad-spectrum cephalosporins. *Antimicrob Agents Chemother* 1994;38:918.
- ① 5. Klugman KP, et al. Randomized comparison of meropenem with cefotaxime for treatment of bacterial meningitis. *Antimicrob Agents Chemother* 1995;39:1140.
- ① 6. de Gans J, van de Beek D, European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. *New Engl J Med* 2002;347:1549-56.
- ② 7. Hasbun R, et al. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *New Engl J Med* 2001;345:1727-33.

PNEUMONIA

Definitions, Etiology, and Epidemiology

- Acute infection of the pulmonary parenchyma associated with symptoms of acute infection, with the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia in a patient not hospitalized or residing in a long-term-care facility for ≥ 14 days before onset of symptoms¹
- Sixth leading cause of death in the United States (most common cause of death due to an infectious disease), with 4 million cases of community-acquired pneumonia (CAP) per year

ETIOLOGY

Organisms	Risk Factors/Clues	Prevalence ²
<i>Staphylococcus pneumoniae</i>	• Most common cause of CAP in all age groups • Advanced age, cigarette smoking, chronic obstructive pulmonary disease (COPD) dementia, malnutrition, chronic illnesses, HIV infection, alcohol abuse, nursing home resident • Bacteremia more common in African Americans and alcohol users	20%-60%
<i>Haemophilus influenzae</i>	COPD/smoker, nursing home resident	3%-10%
<i>Staphylococcus aureus</i>	Elderly, postinfluenza, nursing home resident, IV drug abuse	3%-5%
<i>Moraxella catarrhalis</i>	COPD/smoker	
<i>Streptococcus pyogenes</i>	Associated with empyema	<1%
<i>Neisseria meningitidis</i>		<1%

ETIOLOGY (Continued)

Organisms	Risk Factors/Clues	Prevalence ²
Gram-negatives (including <i>Klebsiella pneumoniae</i> , <i>Pseudomonas</i>)	• Neutropenia, cystic fibrosis, bronchiectasis, HIV, nursing home resident, cardiopulmonary disease, recent antibiotic use, alcohol abuse • Risk factors for <i>Pseudomonas</i>³: structural lung disease (bronchiectasis), steroid therapy, malnutrition, broad-spectrum antibiotic therapy >7 days within past month	3%-10%
Anaerobes	Alcohol abuse, nursing home resident, poor dental hygiene, patients at risk for aspiration, intravenous drug abuse, bronchial obstruction	
<i>Legionella pneumophila</i>	• COPD/smoker • Legionnaire's disease: pneumonia with gastrointestinal (GI) symptoms and high fever, hyponatremia	2%-8%
<i>Mycoplasma pneumoniae</i>	• School-age children, military recruits, college students • May be associated with anemia, Stevens-Johnson syndrome	1%-6%
<i>Chlamydia pneumoniae</i> or <i>psittaci</i>	• Elderly 65–79 years old, nursing home resident • <i>C. pneumonia</i> observed mostly in young people and is very similar to mycoplasma • Exposure to birds, parrots (<i>C. psittaci</i>)	4%-6%
Influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, metapneumovirus		2%-15%

Pearls of the History and Physical Examination⁴

Symptom	Percentage
Fever	80% (Note: may be absent in elderly patients)
Dyspnea	
Cough	
Sputum production	
Rigors	40%-50%
Pleuritic chest pain	30%
Physical Finding	Percentage
Tachypnea	45%-70% (most sensitive sign in elderly patients)
Crackles	80%
Consolidation:	30%
Hypoxia	

- Note that presence of cough, fever, tachycardia, and crackles in the lungs on physical examination has less than 50% sensitivity; therefore, in most instances a chest x-ray is essential for confirming the diagnosis

Diagnostic Studies and Laboratory Values

Blood Tests

- Two sets of bacterial blood cultures recommended in all hospitalized patients with CAP
- Complete blood count: leukocytosis (usually $>15,000$) with left-shift, leukopenia, hemolytic anemia in patients with *Mycoplasma* (positive Coombs' test, increased reticulocyte count, elevated cold-agglutinin titer levels [$>1:64$])⁵
- HIV test recommended by Centers for Disease Control for patients from 15 to 54 years of age hospitalized with CAP in centers with high HIV prevalence rate

- Urinary antigen for *Legionella*: detects *L. pneumophila* serogroup 1; sensitivity 70% and specificity 100%⁶
- Serological studies
 - Legionnaire's disease: fourfold rise in antibody titer to >1:128 (sensitivity 72% if both IgM- and IgG-positive)⁷
 - *Mycoplasma*: complement fixation measuring IgM and IgG, fourfold rise in titer or single titer >1:32 (sensitivity 90%)⁸
- Chemistries: hyponatremia more commonly seen in *Legionella* infection
- Arterial blood gas should be obtained in all patients with severe illness, chronic lung disease³

Chest Radiographic Studies

- Infiltrate on chest radiograph is "gold standard" (lobar consolidation, interstitial infiltrates, cavitation)
- If radiograph is negative but symptoms support pneumonia, repeat radiograph may reveal infiltrate
- Chest computed tomography scan: reserved for patients who fail therapy or develop complications

Sputum Examination

- Send for Gram's stain, and assess for polymorphonuclear (PMN) cells, epithelial cells
 - Acceptable sample: <10 squamous epithelial cells/high power field³ or >25 PMNs and <10 squamous epithelial cells per low power field (LPF)
 - >25 PMNs and <10 epithelial cells/LPF = purulent specimen¹
 - Special stains
 - Acid-fast bacillus (AFB) stains for *Mycobacteria* or *Nocardia*
 - Fluorescent antibody stains for respiratory syncytial virus, adenovirus, parainfluenzaviruses (Sn >80)¹ or *Legionella* (50%-70% Sn)
- Sputum Gram's stain and culture are recommended

by Infectious Diseases Society (IDS) of America in all hospitalized patients with CAP but not recommended by American Thoracic Society (ATS) unless a drug-resistant strain or unusual organism is suspected

Pros of Sputum Culture	Cons of Sputum Culture
Allows for identification of antibiotic sensitivities/resistances of organism for optimization of antibiotic regimen	Difficult to identify colonizer from pathogen
May identify pathogen of epidemiological importance	May not identify one predominant pathogen
May alert physician to "unexpected" or "unusual" organisms	10%-30% of patients with non-productive cough, so difficult to obtain specimen ²
	30%-65% cultures are negative ²
	Interpretation is observer-dependent ³

- Bronchoalveolar lavage, transtracheal aspiration, and transbronchial protected washings are usually reserved for extremely ill or immunocompromised patients who cannot provide sputum sample

Thoracentesis

- When large effusions present (>10 mm on lateral decubitus films) or loculated pleural effusions, enigmatic pneumonias, or fail antibiotic therapy²
- Send for pH (tube on ice), glucose, protein, lactate dehydrogenase, cell count, Gram's stain, AFB stain, culture for bacteria, fungi, and *Mycobacteria*³

Guide to Acute Management

- Decision to admit based on the Pneumonia Patient Outcome Research Team (PORT) prospective cohort study⁹

- Five classes of patients: low mortality (classes I and II) and higher mortality and increasing risk for need for hospitalization or intensive care unit (ICU) stay (classes III-V)
- Scores: I: 0; II: <70; III: 71–90; IV: 91–130; V: >130

Step One: Questions

	Yes	No
Is the patient older than 50 years?	Class II-V	Class I
Any of the following conditions? Active neoplasm, congestive heart failure (CHF), cerebrovascular disease, chronic renal disease, chronic liver disease	Class II-V	Class I
Any of the following physical abnormalities? Altered mental status, pulse rate $\geq 125/\text{min}$, respiratory rate $\geq 30/\text{min}$, systolic blood pressure $< 90 \text{ mm Hg}$, temperature $< 35^\circ\text{C}$ or $\geq 40^\circ\text{C}$	Class II-V	Class I

Step Two: Risk Factors

	Points
Demographic Factors	
Age for men	Age (year)
Age for women	Age (year) – 10
Nursing home resident	+10
Coexisting Illnesses	
Neoplastic disease (active)	+30
Chronic liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Chronic renal disease	+10

(Continued on following page)

	Points
Physical Examination Findings:	
Altered mental status	+20
Respiratory rate ≥ 30 /min	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature $< 35^\circ$ C or $\geq 40^\circ$ C	+15
Pulse ≥ 125 beats/min	+10
Laboratory and Radiographic Findings	
Arterial pH < 7.35	+30
Blood urea nitrogen ≥ 30 mg/dL (11 mmol/L)	+20
Sodium < 130 mmol/L	+20
Glucose ≥ 250 mg/dL	+10
Hematocrit < 30 %	+10
Partial pressure of arterial oxygen < 60 mm Hg	+10
Pleural effusion	+10

Step Three: Add All Points in Step 2 and Assign to a Class

- Class I and II: outpatient therapy
- Class III-V: inpatient therapy
- Factors used in decision-making process not included in PORT criteria: ability to maintain oral intake, GI absorption, medication compliance, history of substance abuse, ability to carry out activities of daily living, cognitive impairment (ultimately, PORT is a supplement to clinical assessment)

Criteria for Admission/Transfer to ICU

- Recommendations from ATS (2001): one of two major criteria or two of three minor criteria³
 - Major criteria: need for mechanical ventilation, septic shock
 - Minor criteria: SBP < 90 mm Hg, multilobar disease, $\text{PaO}_2/\text{FiO}_2 < 250$
- Recommendations from British Thoracic Society: two of four criteria
 - Respiratory rate ≥ 30 /min, diastolic pressure ≤ 60 mm Hg, blood urea nitrogen > 7.0 mmol/L (19.1 mg/dL), and confusion¹⁰

Treatment

- Risk factors for drug-resistant pneumococcus (40% of pneumococci causing CAP): residence in an area with high rates of resistance, age >65 years, alcoholism, noninvasive disease, beta-lactam therapy within 3 months, multiple medical comorbidities, exposure to children in a day care center, immunosuppressive illness³
- Reduced mortality rate at 30 days if hospitalized patient receives first dose of antibiotics within 8 hours of arrival at hospital³
- Empiric therapy to cover both atypical and pneumococcal pneumonia is advised by both the Infectious Diseases Society of America and the ATS
- Duration of therapy³:
 - *S. pneumoniae* and bacterial pneumonia: 7–10 days
 - *M. pneumoniae*, *C. pneumoniae*, and Legionnaire's disease: 10–14 days
 - Do not change antibiotic therapy within first 72 hours unless there is clinical deterioration or bacterial susceptibilities dictate a change
- Switching to oral therapy:
 - ATS criteria³: improved cough and dyspnea, afebrile (<100°F) on two consecutive occasions 8 hours apart, white blood cell count decrease, functional GI tract with adequate oral intake
 - Half of all patients who are clinically stable are eligible for oral switch by the third hospital day

Discharge Criteria

- ATS recommendations³: If no unstable coexisting illnesses or life-threatening complications, then discharge when clinically stable and switching to oral antibiotics; no need to monitor in-house after switching to oral antibiotics; repeat outpatient chest x-ray in 4–6 weeks

- IDS recommendations¹¹: If within past 24 hours patient has no more than one of following criteria:
 - Temperature $>37.8^{\circ}\text{C}$, pulse >100 bpm, respiratory rate >24 breaths/min, systolic blood pressure <90 mm Hg, blood oxygen saturation $<90\%$, and inability to maintain oral intake

EMPIRIC THERAPY

Patient Groups	ATS (2001) ³	IDS (2003 update) ¹¹
Outpatients without other comorbidities	Advanced generation macrolide (azithromycin or clarithromycin), or doxycycline if allergic or intolerant of macrolides	Macrolide (erythromycin, clarithromycin, or azithromycin) or doxycycline <u>If recent antibiotic use:</u> respiratory fluoroquinolone (moxifloxacin, gatifloxacin, levofloxacin, or gemifloxacin) or advanced macrolide (azithromycin or clarithromycin) plus either high-dose amoxicillin (1 g po tid) or advanced macrolide plus high-dose amoxicillin-clavulanate (2 g po bid)
Outpatients with comorbidities	Beta-lactam (po cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin-clavulanate, or IV ceftriaxone) plus macrolide or doxycycline or antipneumococcal fluoroquinolone <u>If nursing home resident or aspiration risk:</u> amoxicillin-clavulanate or amoxicillin <u>Anaerobes or lung abscess present:</u> add clindamycin or metronidazole	Advanced macrolide or respiratory fluoroquinolone <u>If recent antibiotic use:</u> respiratory fluoroquinolone or advanced macrolide plus beta-lactam (high-dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime) <u>If aspiration risk:</u> amoxicillin-clavulanate or clindamycin <u>If patient has influenza with bacterial superinfection:</u> beta-lactam or respiratory fluoroquinolone

EMPIRIC THERAPY (Continued)

Patient Groups	ATS (2001) ³	IDS (2003 update) ¹¹
Inpatient without cardiopulmonary risk factors	IV azithromycin or doxycycline plus beta-lactam or antipneumococcal fluoroquinolone	Respiratory fluoroquinolone or advanced macrolide plus beta-lactam If recent antibiotic use: Advanced macrolide plus beta-lactam or respiratory fluoroquinolone
Inpatient with cardiopulmonary or other risk factors	IV beta-lactam (cefotaxime, ceftriaxone, amoxicillin/sulbactam, high-dose ampicillin) plus IV or po macrolide or doxycycline or IV antipneumococcal fluoroquinolone	Respiratory fluoroquinolone or advanced macrolide plus beta-lactam <u>If recent antibiotic use:</u> advanced macrolide plus beta-lactam or respiratory fluoroquinolone
ICU patients without risk factors for <i>Pseudomonas</i>	IV beta-lactam (cefotaxime, ceftriaxone) plus either IV macrolide (azithromycin) or IV fluoroquinolone	Beta-lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam, or ertapenem) plus either advanced macrolide or respiratory fluoroquinolone <u>Beta-lactam allergy:</u> Respiratory fluoroquinolone with or without clindamycin
ICU patients with risk factors for <i>Pseudomonas</i>	IV antipseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus IV antipseudomonal quinolone (ciprofloxacin) or IV antipseudomonal beta-lactam plus IV aminoglycoside plus either IV macrolide (azithromycin) or IV nonpseudomonal fluoroquinolone	Either antipseudomonal agent (piperacillin, piperacillin-tazobactam, imipenem, meropenem, cefepime) plus ciprofloxacin or antipseudomonal agent plus aminoglycoside plus either respiratory fluoroquinolone or macrolide

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EMPIRIC THERAPY (Continued)

Patient Groups	ATS (2001) ³	IDS (2003 update) ¹¹
		<u>Beta-lactam allergy:</u> Either aztreonam plus levofloxacin or aztreonam plus moxifloxacin or gatifloxacin with or without aminoglycoside
Nursing home resident	Not applicable	Respiratory fluoroquinolone or amoxicillin-clavulanate plus advanced macrolide

Prevention

- Pneumococcal vaccine
 - 65%-84% effectiveness in patients with comorbidities such as diabetes mellitus, cardiovascular disease, chronic pulmonary disease, or status postsplenectomy³
 - Recommendations per ATS³
 - All immune-competent patients >65 years
 - Patients <64 years if they have chronic pulmonary disease, cardiovascular disease, diabetes mellitus, alcoholism, chronic liver disease, CSF leaks, or asplenia or if they are living in special environments (Alaskan natives, American Indian, nursing home resident)
 - Immunosuppressed patients: HIV, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal disease, and 2 weeks before the initiation of immunosuppressive therapy
 - Revaccinate after 5 years if first vaccine received at age <65 years, if immunocompromised, or if asplenic
- Influenza vaccine
 - Usually given September through mid-November
 - Recommendations per ATS³
 - Patients at high risk: all patients >65 years, nursing

- home residents, chronic cardiovascular disease, chronic pulmonary disease, patients with history of multiple hospitalizations within past year, pregnant women in second or third trimester during flu season
- Health-care professionals, nursing home employees, home care providers and household members for patients at high risk, HIV patients, breast-feeding mothers, travelers to foreign countries during influenza epidemics

Antiviral Agents

- Amantadine and rimantadine are active against influenza A: reduces severity of symptoms if given within 48 hours of onset of symptoms; useful for prophylaxis; must be taken for the duration of the epidemic
- Zanamivir and oseltamivir are active against influenza A and B: reduces viral shedding and symptoms by 2 days and prevents secondary complications but must be given within 48 hours of onset of symptoms
- Recommendations of ATS³
 - Prophylaxis for high-risk patients who were vaccinated only after onset of the epidemic, immunodeficient patients, persons caring for high-risk patients, patients in whom vaccination is contraindicated, and patients wanting prophylaxis



Patient Care Warnings

- Administer antibiotics ≤ 8 hours after presentation to reduce mortality risk
- Investigate effusions aggressively in patients who are slow to respond to rule out infected pleural space

References

- ③ 1. Bartlett JG, et al. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2000;31:347-82.
- ③ 2. Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med* 1995;333:1618-24.
- ③ 3. American Thoracic Society Guidelines: Community-acquired pneumonia in adults. *Am J Respir Crit Care Med* 2001;163:1703.
- ③ 4. Metlay JP, et al. Does this patient have community-acquired-pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA* 1997;278:1440.
- ③ 5. Taylor-Robinson D. Infections due to species of *Mycoplasma* and *Ureaplasma*: An update. *Clin Infect Dis* 1996;23:671-84.
- ② 6. Plouffe JF, et al. Reevaluation of the definition of Legionnaire's disease: Use of the urinary antigen assay. *Clin Infect Dis* 1995;20:1286.
- ③ 7. Stout JE, Yu VL. Legionellosis. *N Engl J Med* 1997;337:682.
- ③ 8. Kenny GE, et al. Diagnosis of *Mycoplasma pneumoniae* pneumonia: Sensitivities and specificity of serology with lipid antigen and isolation of the organism on soy peptone medium for identification of infections. *J Clin Microbiol* 1990;28:2087.
- ② 9. Fine MJ, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243.
- ③ 10. The British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults admitted to the hospital. *Br J Hosp Med* 1993;49:346.
- ③ 11. Mandell LA, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 2003;37:1405-33.

NOSOCOMIAL PNEUMONIA

Definitions, Etiology, and Epidemiology

- Hospital-acquired pneumonia (HAP): pneumonia occurring ≥ 48 hours after admission and excluding any infection that is incubating at the time of admission; includes:
 - Health-care-associated pneumonia (HCAP): pneumonia occurring within 90 days of hospitalization in an acute care setting for 2 or more days; indi-

SELECTED RISK FACTORS BY CATEGORY OF HAP

Risk Factor	HAP	HCAP	VAP
Age >70 y	X	X	X
Chronic lung disease/smoking	X	X	X
Altered mental status	X	X	X
Thoracic or abdominal surgery	X	X	X
Supine positioning	X	X	X
Intracranial pressure monitors or nasogastric tubes	X	X	X
Gastric acid suppressive therapy	X	X	X
Parenteral nutrition (due to reflux villous atrophy of intestinal mucosa)	X	X	X
Transfusion of blood products; leukocyte-depleted products may confer less risk ³	X	X	X
Poor inpatient glycemic control	X	X	X
Previous antibiotic exposure	X	X	X
Impaired gag reflex	X	X	X
Gastroesophageal reflux disease (may be worsened by central nervous system depressants [benzodiazepines], anticholinergics)	X	X	X
Immunosuppression (e.g., diabetes, AIDS, glucocorticoid therapy)	X	X	X
Inadequate intensive care unit (ICU) infection control measures	X	X	X
Excessive sedation or paralytics, both of which suppress gag and cough reflexes	X	X	X
Nasotracheal and nasogastric intubation (potential risk of sinusitis)	X	X	X
Residence in extended care facilities or nursing homes		X	
Home infusion therapy		X	
High frequency of community antibiotic resistance		X	
Chronic hemodialysis		X	
Home wound care		X	
Family member(s) colonized with MDR pathogen(s)		X	
Intubation and reintubation			X

cates possible presence of multidrug resistant (MDR) pathogens

- Ventilator-associated pneumonia (VAP): pneumonia developing within 48–72 hours after endotracheal (ET) intubation¹

Hospital-Acquired Pneumonia (HAP)

- Second most common nosocomial infection in United States; very high crude mortality (33%–50%)¹
- In the ICU, 90% of HAP cases occur in the setting of mechanical ventilation
- Late-onset HAP (after first 4 days of hospitalization) carries worse prognosis, with greater likelihood of MDR pathogens
- Microaspiration is considered principle cause in addition to impaired host defenses

Health-Care–Associated Pneumonia (HCAP)

- Awareness of community and institutional resistance patterns is paramount to proper management
- Elderly patients and those with severe underlying disease are disproportionately at risk

Ventilator-Associated Pneumonia (VAP)

- Intubation and mechanical ventilation increase risk of HAP 6–21-fold¹
- Microaspiration of oropharyngeal pathogens into lower airways and leakage of bacteria-containing secretions around endotracheal tube (ET) cuff are the primary routes of pathogenesis²
- May also arise from embolization of infected biofilms in the ET to distant airways³
- More than half of cases are polymicrobial
- Careless disposal of contaminated condensates in ventilator circuits may increase risk, although frequent ventilator circuit changes have not been

shown to decrease risk of VAP, and the patient likely contaminates the circuit, rather than the reverse

Microbiology

- HAP is nearly always caused by bacterial pathogens in immunocompetent hosts; rarely, cause may be fungal or viral (e.g., influenza)
- Polymicrobial infections are not uncommon, particularly in patients with adult respiratory distress syndrome (ARDS)
- Aspiration of anaerobic flora may cause HAP in nonintubated patients but is rare in VAP
- 75% of ICU patients will become colonized with gram-negative bacilli within 48 hours of admission⁴
- *Staphylococcus aureus* is particularly causative in ICU patients as well as those with diabetes or head trauma¹

PREDOMINANT PATHOGENIC BACTERIA IN HAP ⁵	
Organism	Percentage ¹
<i>Pseudomonas aeruginosa</i>	17%
<i>S. aureus</i>	16%
Enterobacteriaceae spp.	11%
<i>Klebsiella</i> spp	7%
<i>Escherichia coli</i>	6%
<i>Haemophilus influenzae</i>	6%
<i>Serratia marcescens</i>	5%
Others: <i>Acinetobacter</i> , <i>Legionella pneumophila</i> viruses (especially influenza), fungi, <i>Streptococcus pneumoniae</i> , anaerobes (<i>Peptostreptococcus</i> , <i>Fusobacterium</i> , <i>Prevotella</i> , and <i>Bacteroides</i>)	

Diagnostic Strategies

- Suspect nosocomial pneumonia in the setting of a new or progressive radiographic infiltrate, plus at least two of the following¹:

- Purulent sputum (>25 polymorphonuclear [PMN] cells with <10 squamous epithelial cells per high power field)
- Presence of a significant respiratory pathogen predominating on Gram's stain
- Peripheral leukocytosis or leukopenia
- Fever $\geq 38^{\circ}\text{C}$ or hypothermia
- Deterioration in gas exchange
- Clinical Pulmonary Infection Score (CPIS)
- Pugin et al devised a diagnostic algorithm in 1990, subsequently adapted by Luna et al⁶ (see the following table)
- Scores >6 predict the presence of HAP with a sensitivity of 77% and a specificity of 42%, although the latter may be increased by the addition of tracheal aspirate cultures
- Repeat score calculations showing improved or persistently low scores at 72 hours (<6) seem to predict those patients who qualify for short courses of antibiotic therapy¹
- Presence of ARDS significantly impairs the utility of the CPIS

SIMPLIFIED CPIS (ADAPTED FROM LUNA ET AL)⁶

Component	Value	Points
Temperature (C)	≥ 36.5 and ≤ 38.4	0
	≥ 38.5 and ≤ 38.9	1
	≥ 39.0 and ≤ 36.0	2
Blood leukocytes/mm ³	≥ 4000 and $\leq 11,000$	0
	< 4000 and $> 11,000$	1
Tracheal secretions	Few	0
	Moderate	1
	Large	2
	Purulent	1
Oxygenation $\text{PaO}_2/\text{FiO}_2$	> 240 or presence of ARDS	0
	≤ 240 and absence of ARDS	1
Chest roentgenogram	No infiltrate	0
	Patchy or diffuse infiltrate	1
	Localized infiltrate	2

- Standard clinical definition of pneumonia (fever, leukocytosis, and purulent tracheobronchial secretions) is reliable in fewer than two-thirds of cases
- In intubated patients, a new or worsening alveolar infiltrate is only 33% specific for VAP
- When clinical criteria are present in the absence of radiographic changes, nosocomial tracheobronchitis should be considered, as antibiotic therapy may still be beneficial in these patients to reduce incidence of subsequent pneumonia
- If ARDS is present, suspicion of HAP should be high, and the presence of only one clinical criterion should prompt further diagnostic testing

Diagnostic Studies and Laboratory Values

- Diagnosis remains challenging and usually requires a combination of clinical and bacteriological strategies

Blood Tests

- Two sets of blood cultures from separate sites
- Complete blood count, serum electrolytes, renal function tests, and liver enzymes
- Oxygen saturation or arterial blood gas if concern for acidosis exists

Radiology

- Chest x-ray posteroanterior and lateral if not mechanically ventilated

Other

- In the presence of a large pleural effusion or any effusion in a toxic patient, diagnostic thoracentesis should be performed to rule out empyema
- If clinical suspicion exists, consider *Legionella* urinary antigen or swab for influenza enzyme immunoassay

- Tracheal aspirate (or bronchoscopic sampling) for Gram's stain, PMN cell count, and culture
- Endotracheal and bronchoscopic cultures¹
 - Bronchoscopic, quantitative cultures of lower respiratory tract secretions carry less risk of inappropriate antibiotics; however:
 - Semiquantitative cultures of endotracheal aspirates rarely fail to contain pathogens found with more invasive measures, and:
 - A properly performed Gram's stain is usually sufficient to guide initial antibiotic therapy
 - A negative tracheal aspirate in a patient without addition or change of antibiotic therapy for 72 hours has a 94% negative predictive value of HAP
 - In VAP, bronchoscopic sampling has been shown to reduce 14-day mortality rate in one study⁷
- Nonbronchoscopic, blind sampling techniques are reasonable options if bronchoscopy is not available
 - Blind bronchial suction has a sensitivity of 74%-97% and a specificity of 74%-100%
 - Blind mini-bronchoscopic alveolar lavage sampling has a sensitivity of 63%-100% and a specificity of 58%-96%
 - Blind protected specimen brush sampling has a sensitivity of 58%-86% and a specificity of 71%-100%
 - Choice of technique should be based on institutional expertise and availability

Guide to Acute Management (From ATS Guidelines)¹

Category of HAP per ATS	Potential Pathogens	Initial Empiric Therapy
Early onset HAP without MDR risk factors	<i>S. pneumoniae</i> <i>H. influenzae</i> Methicillin-sensitive <i>S. aureus</i>	Third-generation cephalosporin, or Fluoroquinolone, or

Category of HAP per ATS	Potential Pathogens	Initial Empiric Therapy
	Antibiotic-sensitive enteric gram-negative rods • <i>E. coli</i> • <i>Klebsiella pneumoniae</i> • <i>Enterobacter</i> spp. • <i>Proteus</i> spp. • <i>S. marcescens</i>	Ampicillin/sulbactam, or Carbapenem
Late onset HAP or other MDR risk factors	Above pathogens, plus MDR pathogens • <i>P. aeruginosa</i> • <i>K. pneumoniae</i> (extended-spectrum beta-lactamases) • <i>Acinetobacter</i> spp. • <i>L. pneumophila</i>	Antipseudomonal cephalosporin, or Carbapenem, or Antipseudomonal beta-lactam/beta-lactamase PLUS Aminoglycoside, or Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) PLUS Linezolid or vancomycin

- Initial therapy should be administered intravenously, with conversion to oral agents when good clinical response is observed and patient has functioning digestive tract (quinolones and linezolid are highly bioavailable)
- Choice of antibiotics should include consideration for local/institutional resistance data
- Patients with HCAP should be treated for MDR pathogens regardless of time of onset of HAP
- Patients who have received recent antibiotics should receive agents from a different class, if possible
- Clinical improvement is usually not seen for 48–72 hours; patients should be clinically reassessed at day 3, unless clinical deterioration occurs

- Narrow antibiotic regimen on the basis of culture data as soon as possible (by day 3)
- A recent study suggests that patients who receive initially appropriate antibiotic regimens may require only 8 days of antibiotic therapy, unless the pathogen is *P. aeruginosa* or *Acinetobacter* spp.
- If *P. aeruginosa* is present, combination therapy is recommended due to high incidence of development of resistance on monotherapy (although combination therapy has not been definitively shown to improve outcomes)⁸
- If extended spectrum beta-lactamase-positive Enterobacteriaceae are present, avoid cephalosporins (consider carbapenem)
- Improvement in oxygenation remains the most reliable predictor of survival



Patient Care Warnings

- Delay of therapy, inappropriate initial therapy, and improper antibiotic dosing are associated with increased morbidity and mortality rates

References

- ③ 1. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia: A consensus statement, American Thoracic Society, October, 2004. *Am J Respir Crit Care Med* 2005;171:388-416.
- ③ 2. Cook D, De Jonghe B, Brochard L, et al. Influence of airway management on ventilator-associated pneumonia. *Ann Intern Med* 1995;122:179-86.
- ② 3. Adair CG, Gorman SP, Feron BM, et al. Implications of endotracheal tube biofilm for ventilator-associated pneumonia. *Intensive Care Med* 1999;25:1072-76.
- ③ 4. Scheld WM. Developments in the pathogenesis, diagnosis, and treatment of nosocomial pneumonia. *Surg Gynecol Obstet* 1991;172(Suppl):42.

- ③ 5. Guidelines for prevention of nosocomial pneumonia. Centers for Disease Control and Prevention. *Respir Care* 1994;39:1191.
- ② 6. Luna CM, Blanzaco D, Niederman MS, et al. Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med* 2003;31:676-82.
- ① 7. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia: A randomized trial. *Ann Intern Med* 2000;132:621-630.
- ① 8. Ibrahim EH, Ward S, Sherman G, et al. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med* 2001;29:1109-15.

CELLULITIS, NECROTIZING FASCIITIS, SUBCUTANEOUS ABSCESS, AND OSTEOMYELITIS

Cellulitis, Necrotizing Fasciitis, and Subcutaneous Abscess

Definition, Etiology, and Epidemiology¹

- Inflammation in the dermis and other subcutaneous tissues in response to bacteria
- Typically caused by skin flora breaching the physical barrier of the epidermis, although can also be caused by hematogenous spread
- Most common organisms are group A beta-hemolytic streptococcus and *Staphylococcus aureus*
- Underlying immunocompromised states (diabetes, cancer, HIV) are important risk factors
- Methicillin-resistant *S. aureus* is now a common community-acquired pathogen in cellulitis and other soft-tissue infections

Pearls of the History and Physical Examination^{1,2}

History

- Fever; skin injury due to trauma, insect, or animal bites; recent surgery
- Nail-biting, pedicures, manicures, local fungal infections (tinea pedis) often serve as portal of entry
- History of coronary artery bypass graft with lower extremity venous graft harvesting
- Patients often unaware of preceding injury

Physical Examination

- Look for erythema, induration, desquamation, bullae, necrotic/foul-smelling tissue, diminished sensation, drainage of pus, and evidence for lymphangitic spread (streaking and/or lymphadenopathy)
- Assess local blood flow (pulses, capillary refill): failure to perfuse is major reason for failure to respond to medical therapy
- Assess extent of necrosis; necrotic tissues requires débridement
- Assess for abscesses: pus collections do not respond to antibiotics and require drainage
- Crepitus on physical examination suggests a gas-forming organism such as *Clostridium perfringens*, particularly in the setting of recent surgery
- Pain out of proportion to examination findings, diminished sensation, and toxic appearance raise concern for necrotizing fasciitis (both community-acquired and postoperative)

Diagnostic Studies and Laboratory Values

Blood Tests

- Complete blood count (CBC): leukocytosis
- Serum chemistries: potassium, renal function tests, and creatine phosphokinase (assess if significant tissue destruction is suspected)

- Blood cultures if lymphedema, fever, or other evidence of systemic infection
- Cultures of needle aspirates (chylis culture) usually not helpful,³ but reasonable to attempt needle aspiration if subcutaneous abscess suspected based on physical examination

Radiology

- Plain films of affected area if gas-forming organism is suspected
- Imaging (magnetic resonance [MRI] or computed tomography) if suspicious for deeper infection such as osteomyelitis, necrotizing fasciitis, or subcutaneous abscess; MRI is most sensitive test for osteomyelitis (see below)

Guide to Acute Management

- Localized infection without evidence of systemic infection can be treated on an outpatient basis with oral antibiotics for 10–14 days
 - Outpatient treatment should be reassessed within 48 hours; progression of infection or lack of improvement is a sign that hospital admission for intravenous (IV) antibiotics may be necessary
- Signs of systemic infection warrant hospital admission for intravenous antibiotics
- Anticipate possible worsening despite appropriate antibiotics for up to 48 hours in immunocompetent hosts and up to 72 hours in diabetic and other immunocompromised patients
- Crepitus, extensive necrotic tissues, or signs/symptoms of poor tissue perfusion on physical examination warrant surgical consultation for possible operative débridement
- In immunocompetent hosts, initial antibiotics (oral or IV) focus on gram-positive streptococci
- Immunocompromised hosts, including diabetics,

warrant broader coverage, including gram-negatives and anaerobes

- Necrotizing fasciitis due to group A streptococcal infections (*S. pyogenes*) treated with penicillin plus clindamycin to inhibit production of toxins and to cover both rapidly dividing and nondividing bacteria (Eagle effect⁴)
- Rates of community-acquired methicillin-resistant *S. aureus* (MRSA) now exceeding 50% in many communities; consult local antibiograms for selection of agents to include coverage for community-acquired MRSA⁵
- Consider infectious disease consultation for cellulitis refractory to IV antibiotic therapy
- Cryptococcus; dimorphic fungi such as histoplasmosis, blastomycosis, and coccidioidomycosis; and atypical mycobacteria⁶ have presented as cellulitis in both immunocompromised and immunocompetent hosts
- Consider home antibiotic therapy as an alternative to prolonged hospitalization⁷; antibiotics with excellent oral bioavailability, such as quinolones, trimethoprim-sulfamethoxazole, doxycycline, minocycline, linezolid, and rifampin, can be used instead of IV antibiotics in certain compliant, reliable patients when infecting organisms are susceptible to these drugs



Patient Care Warnings

- Mark area of inflammation with ink to follow day-to-day progress or resolution of infection
- Elevate and immobilize affected limb
- For lower extremity cellulitis accompanied by limb swelling, consider evaluation for deep venous thrombosis

Osteomyelitis

Definition, Etiology, and Epidemiology⁸

- Bone inflammation of infectious etiology
- Acute hematogenous osteomyelitis most often in children and usually secondary to *S. aureus*
- Subacute and chronic osteomyelitis (1 month and longer) usually associated with open wound or fracture; occurs most often in adults and usually secondary to *Staphylococcus epidermidis*, *S. aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, or *Escherichia coli*
- Immunocompromised state (e.g., diabetes) increases risk of osteomyelitis
- 23% of open fractures associated with deep musculoskeletal infections

Pearls of the History and Physical Examination⁹

History

- Fever and other signs of systemic infection

Physical Examination

- Evidence of local infection, including erythema, localized bone pain, and draining sinus tract
- Palpation of bone or probing bone within ulcer correlates strongly with presence of osteomyelitis¹⁰

Diagnostic Studies and Laboratory Values⁹

- Culture of sinus tract drainage not reliable for diagnosis of causative organism (but usually leads to appropriate antibiotic choice)⁸
- Histopathological diagnosis by microscopic examination is gold standard, but bone biopsy microbiological culture results limited by likely previous antibiotic use¹¹

Blood Tests

- CBC: leukocytosis
- Serum chemistries: elevated erythrocyte sedimentation rate and C-reactive protein

Radiology

- Plain films for initial radiographic screening¹²
 - 14-21 days for changes of acute osteomyelitis to become evident on plain films
- Normal plain films do not exclude presence of osteomyelitis
- Focal accumulation of radioactive tracer on triple-phase technetium bone scan (95% sensitivity)¹³
 - Best test to follow response to therapy
- Magnetic resonance imaging showing bony destruction and/or marrow enhancement¹⁴
 - Excellent anatomic definition that may help surgeons plan débridement
 - Evaluate adjacent soft-tissue involvement
 - Can identify some cases missed by bone scan, particularly when area involved is small
 - Not useful in following response to therapy; MRI changes consistent with osteomyelitis can take up to two years to resolve, despite microbiologic cure

Guide to Acute Management⁸

- Early treatment with intravenous antibiotics for 6-8 weeks (outpatient parenteral antibiotic therapy common)
 - Some evidence that treatment of gram-positive osteomyelitis with linezolid is as good as intravenous therapy¹⁵
 - Prior to community acquired MRSA, oral combinations such as levofloxacin and metronidazole or levofloxacin and clindamycin were used to treat diabetic foot; these do not reliably cover MRSA
 - Consider a combination of medical therapy

- (antibiotics) and surgical resection (débridement of necrotic bone)
- Surgical resection usually reserved for complications (cord compression in vertebral osteomyelitis) or failure of medical therapy
 - Débridement of all necrotic bone often essential in achieving cure of chronic osteomyelitis
 - Prosthetic hardware infection necessitates removal of hardware
 - Revascularization most effective in preventing and treating recurrent osteomyelitis and is often required to prevent poor wound healing and extremity amputation; plastic surgery consultation for “flap procedure” is often indicated in extensive cases
 - Chronic refractory osteomyelitis often requires long-term suppressive therapy with oral antibiotics
 - Local infiltration of antibiotics or implantation of gentamicin beads is commonly done as part of orthopedic débridement procedures.

Organism	First-Line Antibiotic	Alternative Antibiotics
Penicillin sensitive <i>S. aureus</i>	Penicillin G	First-generation cephalosporin
Penicillin-resistant <i>S. aureus</i>	Nafcillin	First-generation cephalosporin
MRSA	Vancomycin	Linezolid, teicoplanin, daptomycin and, in some cases, doxycycline, levofloxacin, TMP-SMX, and rifampin (not to be used as single agent)
Streptococcus	Penicillin G	Levofloxacin, vancomycin, ceftriaxone
Enteric gram-negative rods	Third-/fourth-generation cephalosporin	Quinolones, aminoglycosides, beta-lactam/beta-lactamase inhibitor combinations

(Continued on following page)

Organism	First-Line Antibiotic	Alternative Antibiotics
<i>Serratia</i> , <i>Pseudomonas</i>	Cefepime with at least 2 weeks of aminoglycoside	Imipenem, piperacillin/tazobactam, ceftazidime, all with at least 2 weeks of aminoglycoside
Polymicrobial with anaerobic component	Beta-lactam/beta-lactamase inhibitor combination	Clindamycin or metronidazole plus appropriate aerobic coverage (see above)

References

- ① 1. Swartz MN. Cellulitis. *N Engl J Med* 2004;350:904-12.
- ① 2. Stulberg DL, Penrod MA, Blatny RA. Common bacterial skin infections. *Am Fam Physician*;2002;66:119-24.
- ② 3. Perl B, Gottehrer NP, Raveh D, et al. Cost-effectiveness of blood cultures for adult patients with cellulitis. *Clin Infect Dis* 1999;29:1483.
- ③ 4. Stevens DL, Gibbons AE, Bergstrom R, et al. The Eagle effect revisited: Efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. *J Infect Dis* 1988;158:23-28.
- ② 5. Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med* 2005;352:1436-44.
- ③ 6. Vugia DJ, Jang Y, Zizek C, et al. *Mycobacteria* in nail salon whirlpool footbaths, California. *Emerg Infect Dis* 2005;11:616-18.
- ② 7. Eron LJ, Passos S. Early discharge of infected patients through appropriate antibiotic use. *Arch Intern Med* 2001;161:61.
- ③ 8. Lew DP, Waldvogel FA. Osteomyelitis. *N Engl J Med* 1997;336:999-1007.
- ③ 9. Carek PJ, Dickerson LM, Sack JL. Diagnosis and management of osteomyelitis. *Am Fam Physician* 2002;65:1751.
- ③ 10. Grayson ML, Gibbons GW, Balogh K, et al. Probing to bone in infected pedal ulcers: A clinical sign of underlying osteomyelitis in diabetic patients. *JAMA* 1995;273:721.
- ③ 11. Howard CB, Einhorn M, Dagan R, et al. Fine needle bone biopsy to diagnose osteomyelitis. *J Bone Joint Surg* 1994;76(Suppl B2):311.
- ③ 12. Gold RH, Hawkins RA, Katz RD. Bacterial osteomyelitis: Findings on plain radiography, CT, MR, and scintigraphy. *Am J Roentgenol* 1991;157:365.
- ③ 13. Schauwecker DS. The role of nuclear medicine in osteomyelitis. In Collier DB, Fogelman I, Rosenthal L (eds). *Skeletal Nuclear Medicine*. Mosby, St Louis, 1996.
- ① 14. Karchevsky M, Schweitzer ME, Morrison WB, et al. MRI findings of septic arthritis and associated osteomyelitis in adults. *Am J Roentgenol* 2004;182:119.
- ① 15. Rao N, Ziran BH, Hall RA, et al. Successful treatment of chronic bone and joint infections with oral linezolid. *Clin Orthop Rel Res*. 2004;427:67-71.

ACUTE RETROVIRAL SYNDROME

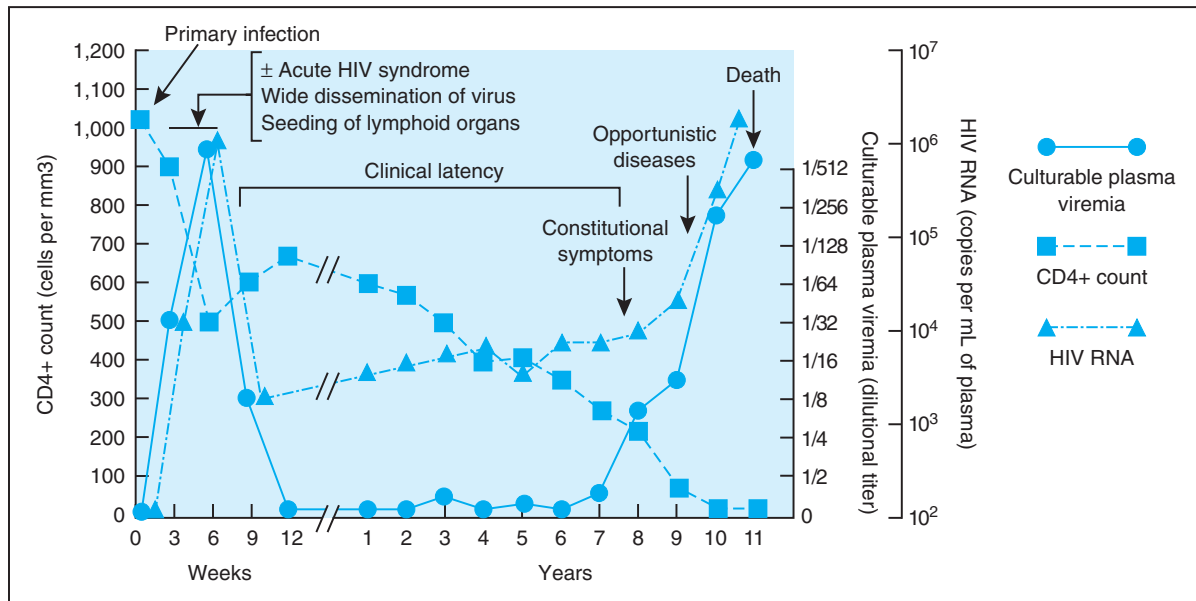
Definition, Etiology, and Epidemiology

- Self-limited, acute mononucleosis-like syndrome associated with primary HIV infection, ranging from mild to severe; symptoms correlate with high-titer HIV-1 viral replication and the host's immune response to this viral invasion¹
- Epidemiology^{2,3}
 - Occurs in 40%-90% of all HIV cases; frequently goes unrecognized (75% of cases)
 - Need to have high level of suspicion in any patient presenting with febrile illness who has risk factors for HIV (including oral-genital contact) or who is presenting with a sexually transmitted infection
 - Route of HIV transmission may present somewhat differently; intravenous (IV) drug users may have milder symptoms; transmitted sexually more likely to produce oral/genital ulcers⁴
- Differential diagnosis: primary cytomegalovirus infection, drug reaction, E-bola virus mononucleosis, viral hepatitis, primary herpes simplex virus infection, influenza, severe streptococcal pharyngitis; secondary syphilis, toxoplasmosis, and rubella.

Pearls of the History and Physical Examination⁵

History

- Incubation: 15-25 days
- More severe symptoms correlate with higher levels of viremia and usually predict a more rapid progression to AIDS⁶
- Duration of illness: from several days to 10 weeks, usually not >14 days

Time course of HIV infection. (Adapted from Pantaleo et al, 1993)⁷

FREQUENCY OF SIGNS AND SYMPTOMS OF ACUTE RETROVIRAL SYNDROME

Sign/Symptom	Frequency (%)
Fever	>80-90
Fatigue	>70-90
Rash (morbilliform/maculopapular)*	>40-80
Headache	32-70
Lymphadenopathy	40-70
Pharyngitis	50-70
Myalgia or arthralgia	50-70
Nausea, vomiting, or diarrhea	30-60
Night sweats	50
Aseptic meningitis	24
Oral ulcers	10-20
Genital ulcers	5-15
Thrombocytopenia	45
Leukopenia	40
Elevated hepatic enzyme levels	21

*A maculopapular skin rash, usually involving the trunk, is highly suggestive of primary HIV infection in a patient at risk

These symptoms are very nonspecific; maintain a high index of suspicion in at-risk patients, and obtain an accurate exposure history

Diagnostic Studies and Laboratory Values

- Complete blood count: lymphopenia, thrombocytopenia, and atypical lymphocytes rare
- Acute HIV infection: negative HIV-1 antibodies with positive HIV RNA or positive p24 antigen
 - Routine HIV antibody tests often negative or indeterminate in acute infection, indicating partial or early antibody response

SENSITIVITY, SPECIFICITY, AND EXPENSE OF DIAGNOSTIC TESTS FOR ACUTE HIV-1

Test	Sensitivity (%)	Specificity (%)	Expense
p24 antigen	88.7	100	\$
HIV-1 RNA	100	97.4	\$\$\$

Guide to Acute Management^{8,9}

- There are no large studies showing a clear clinical benefit from starting highly active antiretroviral therapy (HAART) during acute retroviral illness, but there may be theoretical benefits; most experts recommend referring patient to a study if available

ARGUMENTS IN FAVOR OF AND AGAINST EARLY TREATMENT OF HIV

In Favor	Against
Prevent viral genetic evolution by decreasing HIV replication (and hence HIV mutations, which lead to drug resistance)	Nonadherence to therapy leads to high rates of acquired drug resistance
Destructive nature of HIV infection	Long-term safety of HAART therapy not known; many severe side effects
Potential for immune reconstitution (decrease opportunistic infections)	None
May be able to preserve HIV-specific CD4 response (before all these cells are infected and killed by HIV)	If treatment initiated too early, immune system not able to generate a full response to HIV antigens; some patients may have had a long-term nonprogressive course and instead are committed to potentially toxic drug treatment

- Recent pilot studies suggest that use of immunosuppression (e.g., cyclosporin A) in conjunction with HAART may help preserve virus-specific cellular immunity¹⁰
- Before initiating treatment, determine likelihood of patient compliance and discuss treatment options with patient
- Long-term studies needed to help clarify issue of early treatment

References

- ③ 1. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *N Engl J Med* 1998;339:33-39.
- ③ 2. Clark SJ, Shaw GM. The acute retroviral syndrome and the pathogenesis of HIV-1 infection. *Semin Immunol* 1993;5:149-55.
- ③ 3. Hansasuta P, Rowland-Jones SL. HIV-1 transmission and acute HIV-1 infection. *Br Med Bull* 2001;58:109-27.
- ② 4. Routy JP, et al. Comparison of clinical features of acute HIV-1 infection in patients infected sexually or through injection drug use. *J Acquir Immune Defic Syndr* 2000;24:425-32.
- ② 5. Schacker T, et al. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med* 1996;125:257-64.
- ② 6. Vanhems P, Lambert J, Cooper DA, et al. Severity and prognosis of acute human immunodeficiency virus type 1 illness: A dose-response relationship. *Clin Infect Dis* 1998;26:323-29.
- ② 7. Pantaleo G, Graziosi C, Fauci AS. New concepts in the immunopathogenesis of human immunodeficiency virus infection. *N Engl J Med* 1993;328:327-35.
- ③ 8. Burman WJ, Reves RR, Cohn DL. The case for conservative management of early HIV disease. *JAMA* 1998;280:93-95.
- ③ 9. Walker BD, Basgoz N. Treat HIV-1 infection like other infections—treat it. *JAMA* 1998;280:91-93.
- ① 10. Rizzardi GP, et al. Treatment of primary HIV-1 infection with cyclosporin A coupled with highly active antiretroviral therapy. *J Clin Invest* 2002;109:681-88.

PCP AND OTHER HIV-RELATED PULMONARY DISEASES

Definitions, Etiology, and Epidemiology

EPIDEMIOLOGY OF PULMONARY DISEASE IN HIV PATIENTS BY PATHOGEN¹

Fungal	• <i>Pneumocystis carinii</i> pneumonia (PCP) has been reclassified as a fungus and renamed <i>Pneumocystis jiroveci</i>; it is the most common AIDS-defining opportunistic infection, although its incidence has much decreased since advent of highly active antiretroviral therapy (HAART) • 15%-28% of HIV-positive patients develop PCP annually • Histoplasmosis increased if patient lived or traveled to Mississippi River Valley • Coccidiomycosis increased if patient lived or traveled to southwest United States
Bacterial ²	• Bacterial pneumonia >3-5 times more common in HIV-positive patients than in HIV-negative patients • Among HIV-positive, those with intravenous (IV) drug use, low CD4 count, and prior PCP are at higher risk for bacterial pneumonia • Treatment with HAART decreases risk of bacterial pneumonia • Atypical pneumonia appears to be relatively uncommon in HIV
Tuberculosis (TB)	• HIV-positive patients have higher rates of reactivation disease (7%-10%/y vs. 8%/lifetime), acute disease (37%/6 mo vs. 5%/2 y), skin anergy and extrapulmonary TB than HIV-patients³
Viral	• More common in IV drug users with HIV • May see more influenza in HIV-positive patients

EPIDEMIOLOGY OF PULMONARY DISEASE IN HIV PATIENTS BY PATHOGEN¹ (Continued)

Effect of prophylaxis/ vaccination	• Cytomegalovirus (CMV) as a pathogen is controversial; studies from the pre-HAART era often found CMV in respiratory specimens, but it was usually associated with another primary pathogen; often responds to treatment of the primary pathogen alone
	• HHV-8–related Kaposi's sarcoma seen almost exclusively in HIV-positive men who have sex with men
	• TMP/SMX decreases incidence of PCP as well as bacterial pneumonia
	• Influenza vaccine decreases incidence of influenza
	• Pneumovax not as protective in HIV-positive individuals

Pearls of the History and Physical Examination

CLINICAL PRESENTATION OF DIFFERENT PATHOGENS IN HIV^{4,5}

Common Pathogens	Clinical Presentation	CD4 count (cells/ μ L)
Fungal		
PCP	Insidious onset of fever, sweats, cough (usually nonproductive), progressive dyspnea (average of 3 weeks symptoms)	<200
<i>Aspergillus</i> , coccidiomycosis, histoplasmosis	Subacute, fever, night sweats, cough, dyspnea	<200 and often <50, also if neutropenic
Cryptococcus	Subacute, cough, fever, 80% have meningitis	<50

(Continued on following page)

CLINICAL PRESENTATION OF DIFFERENT PATHOGENS IN HIV^{4,5} (Continued)

Common Pathogens	Clinical Presentation	CD4 count (cells/ μ L)
Protozoan		
Toxoplasma, strongyloides, cryptosporidium, and microsporidium (rare pulmonary pathogens)	Similar to PCP	Similar to PCP
Bacterial		
<i>Staphylococcus pneumoniae</i> , <i>Haemophilus</i> , <i>Moraxella</i> , <i>Klebsiella</i> , <i>Neisseria meningitides</i> , <i>Rhodococcus</i> , <i>Staphylococcus aureus</i> , <i>Nocardia</i> , <i>Legionella</i> , <i>Pseudomonas aeruginosa</i>	Abrupt fever or chills, productive cough, pleuritic chest pain, dyspnea	Any CD4 count; more common as CD4 count decreases; <i>Nocardia</i> , <i>P. aeruginosa</i> if CD4 <50
Mycobacterial		
TB	Fever, weight loss, fatigue; if higher CD4 count, may see classic symptoms (hemoptysis and cough)	Any CD4 count; more common as CD4 decreases
Atypical mycobacteria (relatively uncommon): <i>Mycobacterium avium</i> complex (also <i>M. fortuitum</i> , <i>M. goodii</i> , <i>M. kansasii</i> , etc.)	Fever, weight loss, lymphadenopathy; subacute, may be asymptomatic	<50

CLINICAL PRESENTATION OF DIFFERENT PATHOGENS IN HIV^{4,5} (Continued)

Common Pathogens	Clinical Presentation	CD4 count (cells/ μ L)
Viral		
CMV pneumonitis	Fevers and chills, night sweats, dyspnea (similar to PCP)	<50-100
Influenza	Fever, headache, malaise, myalgias, nonproductive cough	Any CD4 count
Miscellaneous		
Sinusitis/bronchitis: <i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>P. aeruginosa</i> , <i>Cryptococcus</i> , <i>Alternaria</i> , <i>Aspergillus</i> , <i>Bipolaris</i>	Congestion, facial and retro-orbital pain, headache, fever of unknown origin	Any CD4 count; more common as CD4 decreases; chronic infection and <i>P. aeruginosa</i> more common if CD4 <50
Kaposi's sarcoma	Dry cough, dyspnea, hemoptysis, skin lesions	Any CD4 count; more common as CD4 decreases
Nonspecific interstitial pneumonitis	Resembles PCP	Normal
Lymphoma	Subacute, shortness of breath (SOB)	Any CD4 count
Lymphocytic interstitial pneumonia	Less common in adults, cough, progress; SOB, parotid enlargement	200-400

- Consider HAART therapy when establishing differential diagnosis:
 - If HAART was initiated within the last several months, consider immune reconstitution (including noninfectious etiologies such as sarcoidosis)
 - PCP is less common and bacterial infections are more common in the post-HAART era

Physical Examination

- Should include lung examination, full lymph node survey, fundoscopy, and skin examination
- 50% of patients with PCP may have normal lung examination results

Diagnostic Studies and Laboratory Values

CHEST X-RAY FINDINGS OF HIV-ASSOCIATED DISEASES⁶

	Common	Less Common
PCP (fungal)	Diffuse bilateral interstitial or alveolar infiltrates ("ground glass")	Pneumothorax, lobar or segmental infiltrates, cysts, nodules, apical infiltrates (if receiving aerosolized pentamidine); pleural effusions and hilar adenopathy are rare with PCP and should prompt another diagnosis
Bacterial	Lobar or segmental infiltrate, air bronchograms	Diffuse infiltrates (<i>Haemophilus</i>); upper lobe consolidation or cavitation, with or without pleural or pericardial effusion (<i>Nocardia</i> , <i>Rhodococcus</i>)
Mycobacterial (<i>M. tuberculosis</i>)	Upper lobe consolidation or cavitation (if CD4 >200)	Intrathoracic adenopathy, lower lobe infiltrates, pleural effusion (if CD4 >200); normal chest x-ray (in 10%-20% with AIDS)
Viral (CMV)	Bilateral peribronchovascular and alveolar process (CMV)	Focal consolidation

CHEST X-RAY FINDINGS OF HIV-ASSOCIATED DISEASES⁶ (Cont'd)

	Common	Less Common
Fungal	Diffuse infiltrates	Thin-walled cavities (coccidiomycosis), adenopathy, pleural effusions; consolidation (<i>Cryptococcus</i>)
Kaposi's sarcoma	Patchy nodules, pleural effusion, hilar lymphadenopathy	Reticulonodular infiltrates
Lymphoma	Hilar lymphadenopathy	Pleural effusion
Lymphocytic or nonspecific interstitial pneumonitis	Diffuse interstitial infiltrates	

If a patient with PCP has lymphadenopathy, consider additional diagnoses

- Chest computed tomography (CT)
 - More sensitive than radiograph to detect early disease
 - High-resolution CT has a high sensitivity for PCP
- Nuclear scanning: gallium-67 scanning sensitive for PCP but not specific (may see uptake with lymphoma, but not Kaposi's sarcoma)
- Exercise-induced oxygen desaturation: sensitive, noninvasive; high negative predictive value for PCP
- Diffusing capacity of the lung for carbon monoxide: sensitive but not specific for PCP; high negative predictive value
- Bronchoscopy with BAL with or without trans-bronchial biopsy (consider if unable to obtain sputum or sputum is nondiagnostic)
- Surgical or CT-guided lung biopsy: consider if bronchoscopy and BAL are nondiagnostic, but this carries higher complication/morbidity rate

DEFINITIVE DIAGNOSIS OF PULMONARY PATHOGENS IN HIV

PCP	Sputum (specificity of immunofluorescent antibody 100%, sensitivity 55%-92%); elevated lactate dehydrogenase (sensitive, not specific); bronchoalveolar lavage (BAL) is the gold standard (90%-95% sensitive)
Bacterial	Sputum culture, occasionally blood culture (especially with <i>S. pneumoniae</i>)
Mycobacterial ⁷	• Acid-fast bacilli (AFB) stain sputum 30%-89% positive in TB, AFB culture of sputum 85%-100% positive in TB • Induce sputum if patient unable to produce; yield of sputum is also fairly high in TB pleuritis; polymerase chain reaction helpful <i>only</i> in AFB smear; positive sputum to determine species • Purified protein derivative skin test (often anergic if CD4 <300)
Viral	May see CMV on BAL (CMV in sputum is a rare cause of pneumonia; must be seen on transbronchial biopsy)
Fungal	Urine histoplasma antigen (for disseminated disease); serum cryptococcal antigen (specific, not sensitive if disease is localized), can follow titers to monitor disease in both cases

Guide to Acute Management

TREATMENT OF HIV-ASSOCIATED PULMONARY DISEASES

	Treatment	Alternative
PCP**	TMP/SMX 15-20 mg/kg/d IV or po tmp divided 3-4 times/d × 21 days or Dapsone 100 mg + TMP 5 mg/kg/d po tid × 21 days and corticosteroids if PaO₂ <70 or A-a gradient >30 (prednisone 40 mg po bid × 5 days, 40 mg po qd × 5 days, then 20 mg po qd × 11 days)	Clindamycin 450-900 mg IV or po qid + primaquine 15 mg po qd for 21 days or Atovaquone suspension 750 mg po bid × 21 days or pentamidine 4 mg/kg/d IV × 21 days

TREATMENT OF HIV-ASSOCIATED PULMONARY DISEASES (Cont'd)

	Treatment	Alternative
Bacterial	(Treat the same as in general population) If not hospitalized from community-acquired: macrolide If hospitalized from community-acquired: 3rd-generation cephalosporin + macrolide If hospital-acquired: Carbapenem or Antipseudomonal penicillin + antipseudomonal aminoglycoside or 3rd-generation + antipseudomonal aminoglycoside cephalosporin +/- clindamycin	2nd- or 3rd-generation cephalosporin, fluoroquinolone Fluoroquinolone Ticarcillin/clavulanate or piperacillin/tazobactam + ciprofloxacin
Mycobacterial ⁷	TB (four-drug therapy): Isoniazid 300 mg po qd + Rifampin* 600 mg po qd + ethambutol 15 mg/kg/d + pyrazinamide 25 mg/kg/d • In HIV, first 2 months should be at least 3x/week • For isolated pulmonary disease, treat for at least 6 months ALL TB patients need to have directly observed therapy MAC: clarithromycin 500 mg po bid (or azithromycin) + ethambutol 15 mg/kg/d +/- rifabutin 300 mg po qd or ciprofloxacin 500 mg po bid	If multidrug-resistant TB: Consult an ID specialist; need at least four drugs likely to be effective, one of them parenteral (e.g., streptomycin) for 2 years (other possible medications: capreomycin, fluoroquinolones)
Viral	(If within first 48 hours of illness): Influenza A/B: oseltamivir 75 mg po bid x 5 days or zanamivir 2 inhalations bid x 5 days	Only for influenza A: amantadine/rimantidine 100 mg po bid (unless patient over 65 years, then 100 mg po qd; adjust for renal clearance)

(Continued on following page)

TREATMENT OF HIV-ASSOCIATED PULMONARY DISEASES (Cont'd)

	Treatment	Alternative
	CMV (treat only if biopsy-proven): ganciclovir 5 mg/kg IV $\times$ 2 weeks, then chronic suppression with 5 mg/kg/d	Foscarnet 90 mg/kg IV q12h $\times$ 2 weeks, then maintenance 90-120 mg/kg/d
Fungal**	Coccidiomycosis: Mild-moderate disease: itraconazole 200 mg po/IV bid OR fluconazole 400 mg po qd for 3-12 months; then fluconazole 200 mg po qd	Severe disease: amphotericin B 0.6-1 mg/kg/d IV $\times$ 7 days, then 0.8 mg/kg/qod, total dose 2.5 g, followed by itraconazole or fluconazole as per mild disease
	Histoplasmosis: Amphotericin B 0.6-1 mg/kg/d IV $\times$ 14 days, followed by itraconazole 200 mg po qd	Mild to moderate disease: Itraconazole 300 mg po bid $\times$ 3 days, then 200 mg po bid $\times$ 12 weeks, then 200 mg po qd
	Cryptococcosis: Amphotericin B 0.7-1 mg/kg/d IV + 5-flucytosine 25 mg/kg/q6h po $\times$ 2 weeks, then fluconazole 400 mg po qd $\times$ 10 weeks, then fluconazole 200 mg po qd	Fluconazole 400 mg po qd $\times$ 6-10 weeks, then 200 mg po qd
	Aspergillosis: Amphotericin B 1 mg/kg IV qd total 2.5 g (consider lipid amphotericin B product at 5 mg/kg/d), then fluconazole 300 mg po tid $\times$ 4d, then 200 mg po bid	Caspofungin 70 mg IV on day 1, then 50 mg IV qd or Voriconazole 6 mg/kg IV q12h on day 1, then 200 mg po bid or 4 mg/kg IV bid
Other	Kaposi's sarcoma	HAART = first-line therapy; chemotherapy: liposomal daunorubicin/doxorubicin; taxol; adriamycin, bleomycin/vincristine, or vinblastine
	Lymphocytic interstitial pneumonia	Prednisone?
	Lymphoma	CHOP, others

*Many HIV medications (protease inhibitors and nonnucleoside reverse transcriptase inhibitors) interact with rifampin; use rifabutin instead and adjust dose; note that the weekly rifapentine regimen is associated with an increased rate of relapse in HIV-positive patients.

**These are acute regimens that are listed; note that immunosuppressed patients will often need lifelong suppressive therapy after infection is treated (e.g., fluconazole in all the fungal infections).



Patient Care Warnings

- AIDS patients, especially if they have a low CD4 count, may present with more than one opportunistic infection simultaneously
- Treating their HIV is as important as treating their opportunistic infections

References

- ② 1. Wallace JM, et al. Respiratory disease trends in the pulmonary complications of HIV infection study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med* 1997;155:72-80.
- ② 2. Hirschtick RE, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med* 1995;333:845-51.
- ③ 3. Sepkowitz KA, et al. Tuberculosis in the AIDS era. *Clin Microbiol Rev* 1995;8:180-99.
- ② 4. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. *Chest* 2001;120:1888-93.
- ② 5. Hoover DR, et al. Clinical manifestations of AIDS in the era of *Pneumocystis* prophylaxis. Multicenter AIDS Cohort Study. *N Engl J Med* 1993;329:1922-26.
- ③ 6. Bartlett JEA. Medical Management of HIV Infection. Baltimore, Johns Hopkins University, 2003.
- ③ 7. Leads from the MMWR. Tuberculosis and acquired immunodeficiency syndrome—New York City. *JAMA* 1988;259:338-45.

IMMUNE RECONSTITUTION SYNDROME

Definitions, Etiology, and Epidemiology

- Immune reconstitution syndrome (IRS); also known as immune restoration disease, immune reconstitution inflammatory syndrome

- Paradoxical decline in clinical status due to the recovery of the immune system during highly active antiretroviral therapy (HAART)¹
- Suppression of viral replication and restoration of immune function (CD4 count increase) allow restoration of previously suppressed host immune response to copathogens (mycobacteria, cryptococcus, cytomegalovirus [CMV], etc.)¹
- Cytokines as well as an increase in CD8+ cells also appear to play a role²

Epidemiology

- 25% of HIV patients affected that respond to HAART (regardless of whether they were HAART-naïve or restarting HAART)
- Most patients who develop IRS have a low CD4 count (<50) before HAART initiation
- Average time of onset is 8-12 weeks after starting HAART
- May not have symptoms of opportunistic infection before HAART
- IRS more common when treated with protease inhibitor
- Patients may develop IRS from a pathogen despite prophylactic medication

Pearls of the History and Physical Examination

- Other less common diseases that may present as IRS: sarcoidosis, Kaposi's sarcoma, lymphoma, *Bartonella henselae*, Graves' disease, *Pneumocystis jiroveci* pneumonia, molluscum contagiosum, Reiter's syndrome, leprosy
- With some of these diseases, may see the typical clinical scenario when presenting as IRS; others may have very atypical clinical features; the key is to consider the possibility of IRS in any patient who was recently started on HAART

SYMPTOMS AND CHARACTERISTICS OF IRS IN VARIOUS HIV-ASSOCIATED CLINICAL SYNDROMES^{3,4}

Disease	Typical Symptoms/ Signs	Symptoms/ Signs in IRS	Time of Onset	Other Characteristics
<i>Mycobacterium avium complex</i> (MAC)	Disseminated disease, mycobacteremia, weight loss, diarrhea, fever, abdominal pain	Lymphadenitis; unusual to have mycobacteremia or wasting; rarely seen: subcutaneous nodules, endobronchial tumor, paravertebral abscess	Majority within 1 month, described up to 32 months	Granulomas with caseation: suggests restored inflammatory response
<i>Mycobacterium tuberculosis</i> (MTB)	Fever, cough, hemoptysis, weight loss	Fever, cough, lymphadenopathy; cecitis, MTB in central nervous system (tuberculoma), disseminated MTB	10-180 days	TB skin test (Mantoux) may go from anergic to positive
<i>Cryptococcus neoformans</i>	Indolent meningitis, cerebrospinal fluid (CSF) leukocytosis uncommon	Acute meningitis, CSF leukocytosis; subcutaneous abscesses, lymphadenitis, necrotizing pneumonia	Meningitis: within 2 weeks; Lymphadenopathy: average 9 months	Positive cryptococcal Ag; can see IRS even without viable organisms
CMV	In eye, retinitis with minimal inflammation	Vitritis, retinitis, uveitis with marked inflammation; parotitis, pneumonitis, colitis	2 weeks-6 months	After recovery from IRS, may see a long-lasting disease remission

(Continued on following page)

SYMPTOMS AND CHARACTERISTICS OF IRS IN VARIOUS HIV-ASSOCIATED CLINICAL SYNDROMES^{3,4} (Continued)

Disease	Typical Symptoms/ Signs	Symptoms/ Signs in IRS	Time of Onset	Other Characteristics
Herpes zoster	May see severe disease with complications	Less severe, dermatomal zoster, iritis, keratitis	Most within 16 weeks	2-5 times increase in herpes zoster in HIV patients treated with HAART
Herpes simplex	Mucocutaneous herpes lesions	Mucocutaneous herpes lesions, myelopathy, encephalopathy	Most within 8 weeks	May not have previous history of herpes
Hepatitis B/C (HBV/HCV)	Hepatitis	Elevated liver enzymes, especially alanine aminotransferase; cirrhosis, can see cryoglobulinemia with HCV	Several weeks to months	Patients may change from HCV antibody-negative to antibody-positive; often need liver biopsy to distinguish IRS from drug hepatotoxicity
Progressive multifocal leukoencephalopathy (PML)	Neurological deficits, magnetic resonance image (MRI) with hypodensities, no enhancement	MRI hypodensities, with peripheral contrast enhancement; inflammatory PML	6-8 weeks	Unlike usual PML, PML from IRS will show improving or stable neurological findings

Diagnostic Studies and Laboratory Values

- No strict clinical criteria: look for all causes of symptoms, particularly infectious causes; consider drug toxicity as a cause; check CD4, viral load
- IRS associated with:
 - Low (<100, usually <50) baseline CD4 count
 - Decrease in HIV RNA after starting HAART >1 log copies/mL, which confirms that the disease seen is not the result of a delayed immunological or virological response
 - Change in titers or antibodies to pathogen (e.g., hepatitis serologies, HCV/HBV viral load, cryptococcal antigen, purified protein derivative) that were tested prior to initiation of HAART¹

Guide to Acute Management

- No established guidelines as most data on IRS are anecdotal
- Consensus is to continue HAART therapy if patient tolerates it
- Start antimicrobials for pathogen identified

SUCCESSFUL TREATMENT OF IRS

Infection	Treatment
MAC	Corticosteroids, antimycobacterial therapy, local surgical drainage
MTB	Anti-inflammatory agents and antituberculous therapy; may need to hold HAART until anti-TB medications have decreased organism burden
<i>Cryptococcus neoformans</i> , <i>Histoplasma capsulatum</i>	Antifungal chemotherapy; treat intracranial hypertension with either serial lumbar punctures or lumbar peritoneal drains

(Continued on following page)

SUCCESSFUL TREATMENT OF IRS *(Continued)*

Infection	Treatment
CMV	Topical medication, periocular steroids, anti-CMV therapy
Herpes zoster	Anti-herpesvirus chemotherapy
Herpes simplex virus	Anti-herpesvirus chemotherapy
HVC	Interferon A, discontinuation of HAART
HVB	Continuation of HAART; discontinuation of HAART
PML	Continuation of HAART

*If symptoms of IRS are severe or if CNS involved, corticosteroids may need to be added. Adapted from DiSimone.³

**Patient Care Warnings**

- Prevention
 - Caution when initiating antiretroviral therapy in patients with ongoing opportunistic infections.
 - Current recommendations are to delay initiation of HAART for 1 or 2 months after initiation of anti-TB, MAC, or cryptococcosis therapy

References

- ③ 1. Shelburne SA, et al. Immune reconstitution inflammatory syndrome: Emergence of a unique syndrome during highly active antiretroviral therapy. *Medicine (Baltimore)* 2002;81:213-27.
- ② 2. Price P, et al. Polymorphisms in cytokine genes define subpopulations of HIV-1 patients who experienced immune restoration diseases. *Aids* 2002;16:2043-47.
- ③ 3. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. *Ann Intern Med* 2000;133:447-54.
- ② 4. French MA, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med* 2000;1:107-15.

TUBERCULOSIS

Definition, Etiology, and Epidemiology

- Tuberculosis (TB) endemic in most developing countries; increasing incidence associated with high rates of HIV infection
- Includes both pulmonary (most common) and extrapulmonary pathology
- Causative agents: *Mycobacterium tuberculosis* complex, consisting of *M. tuberculosis*, *M. bovis* (less common), and *M. africanum* (rare)
- Ziehl-Neelsen (or auramine-rhodamine) stain reveals acid-fast bacilli (AFB) due to the presence of cell wall mycolic acid, which promotes resistance from lysosomal degradation after phagocytosis by macrophages; cytokine (tumor necrosis factor) production by the infected cells attracts other phagocytic cells, leading to granuloma formation
- Chronic suppressive, nonbactericidal defense leads to development of organized layers of macrophages and lymphocytes surrounding a core of AFB (i.e., granuloma), often with central necrosis or caseation
- Primary TB
 - Inhalation of bacilli leads to replication in dependent lobes of the lung: primary focus; symptoms result from local infection and host reaction; usually a benign course as the intact immune system is able to suppress growth of the organism and prevent progression of disease
 - Consequently, patients with weaker immune systems (e.g., children and HIV-positive patients) will predominantly display features of primary TB
 - Primary infection can lead to:
 - Healing
 - Progressive local disease (pleurisy, pneumonia, cavitation)

- Lymphohematogenous dissemination, with granuloma formation in most organs and bone marrow (miliary TB); this presentation is chronic or subacute, therefore not discussed extensively in this section
- Secondary (post-primary) TB
 - Reactivation of latent TB in individuals who initially suppressed growth of the organism; it can occur years, even decades, after initial exposure
 - Can be spread as aerosolized droplets released during coughing, sneezing, and talking
 - Risk factors include residence or travel in developing countries, poverty, incarceration, silicosis, diabetes, end-stage renal disease, malnutrition, and immunosuppression (children, HIV, transplant, malignancy)

Pearls of the History and Physical Examination

- Fever, night sweats, fatigue, weight loss, productive cough, blood-streaked sputum, TB contacts or risk factors

Diagnostic Studies and Laboratory Values

Chest X-Ray

- Primary TB: peripheral pulmonary infiltrate anywhere in the lung with perihilar lymphadenopathy (i.e., Ghon's complex), often accompanied by an effusion when organisms invade the pleural space
- Secondary TB: infiltrates usually in better oxygenated areas of the lung: upper, posterior, and superior lower lobes; calcifications of granulomas might also be seen
- 30% of patients have classic radiographic findings, so any abnormal radiograph with a strong clinical suspicion should warrant further workup

Purified Protein Derivative (PPD)

- Positive if >5 mm in HIV-positive patients; patients with recent close TB contact; apical fibrotic lesions on chest x-ray; transplant and immunosuppressed patients
- Positive if >10 mm in high-risk patients (recent immigrants, IV drug use, health-care workers)
- Positive if >15 mm in low-risk patients
- Positive if anergy testing not recommended as being useful for HIV-positive patients¹

Sputum

- Sputum AFB smears: morning induced sputum samples for 3 consecutive days have yield of 91%²; 3 negative smears usually indicate a *noninfective* patient (not necessarily uninfected)
- Sputum AFB culture: three consecutive morning sputum sample cultures have yield of 99%²

Biopsy

- Pleural biopsy: especially useful for presence of granulomas on pathology as pleural fluid AFB smear/cultures are rarely positive
- Pericardial biopsy: similar to pleural biopsy

M. tuberculosis Amplification

- Polymerase chain reaction (PCR) studies emerging with higher sensitivity, especially for cerebrospinal fluid (CSF), but not yet widely available

Important

- The definitive diagnosis of pulmonary tuberculosis relies on identifying or culturing *M. tuberculosis* from respiratory specimens
- Extrapulmonary disease is often diagnosed without

microbiological confirmation; the pathogenesis of TB meningitis is thought to be due to exuberant immune reaction rather than chronic infection

Guide to Acute Management

Active TB

- Initial phase consists of 2 months of rifampin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB); start treatment if patient AFB-positive, if clinical suspicion high despite initial negative smears, or if patient is clinically ill in the absence of other diagnoses; can stop EMB therapy if isolate returns sensitive before 2 months³
- At 2 months:
 - If repeat smear is negative and isolate is sensitive, continue daily or twice weekly RIF + INH for 4 more months⁴
 - In HIV-positive ($CD4 < 100$) patients, must have daily RIF + INH⁵
 - If INH not feasible (e.g., liver disease or resistance), RIF + PZA + EMB therapy daily for 6 months is just as efficacious⁶
 - If repeat smear results are negative, isolate sensitive, HIV-negative, and no cavitation on radiograph, can use once weekly rifapentine + INH for four more months⁷
 - If repeat smear results are positive and radiograph without cavitation, same as continue daily or twice weekly RIF + INH for 4 more months⁴
 - If repeat smear results are positive and chest x-ray with cavitation, RIF + INH for 7 more months³
- Substitute rifabutin for rifampin in HIV patients taking antiretrovirals⁸

Culture-Negative TB

- Infectious Disease Service consultation highly recommended if this scenario is suspected

- Defined as negative sputum AFB smear/culture with a positive PPD, abnormal radiograph results, and clinical suspicion; important to treat as 17% of new TB cases in United States are culture-negative⁹
- Initiate four-drug regimen; at 2 months, if clinical course or radiograph improves in absence of other diagnosis, continue RIF + INH an additional 2 months³

Latent TB

- Defined as PPD-positive without clinical symptoms or significant radiographic abnormalities
- INH daily for 9 months preferred¹⁰ but 6-month regimen also shown to be adequate¹¹ and perhaps more cost-effective¹²; HIV-positive patients recommended for 9 months¹⁰
- RIF + PZA therapy no longer recommended due to hepatotoxicity¹³
- RIF daily for 4 months for patients with silicosis or unable to tolerate INH¹⁴
- Distinguish latent TB from culture-negative TB before starting monotherapy so as not to risk emergence of INH-resistant TB

Extrapulmonary TB

- Treatment guidelines/duration are the same as for pulmonary TB, with the following considerations:
 - Pericarditis requires 11 initial weeks of steroid therapy with a 6-month regimen^{15,16}
 - Osteomyelitis (e.g., Pott's disease) adequately treated with rifampin-containing regimen, but surgical débridement offers no additional benefit¹⁷
 - Pleuritis adequately treated with 6-month regimen and complete drainage of effusion, but steroids offer no additional benefit¹⁸
 - Meningitis treatment recommended for 9-12 months (based on clinical experience rather than studies), with initial course of dexamethasone¹⁹;

repeat CSF studies recommended to assess success of treatment³

- Renal TB is rare and difficult to diagnose, but treated adequately with pulmonary regimen



Patient Care Warnings

- Rare but serious complications in the antituberculous agent era
 - Rasmussen's aneurysm: causes sudden massive hemoptysis (TB erodes into the bronchial vessels)
 - Pneumothorax
- Pyridoxine supplementation with INH; obtain baseline and follow-up laboratory tests, specifically liver enzymes; follow visual acuity and red-green color discrimination for patients on EMB

References

- ③ 1. Centers for Disease Control and Prevention. Anergy skin testing and tuberculosis preventive therapy for HIV-1 infected persons: Revised recommendations. *Morb Mortal Wkly Rep* 1997;46:1-10.
- ① 2. Al Zahrani K, Al Jahdali H, Poirier L, et al. Yield of smear, culture and amplification tests from repeated sputum induction for the diagnosis of pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2001;5:855-60.
- ③ 3. American Thoracic Society/Centers for Disease Control and Prevention/Infection Diseases Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med* 2003;167:603-62.
- ① 4. British Thoracic Association. A controlled trial of six months' chemotherapy in pulmonary tuberculosis: Second report results during the 24 months after the end of chemotherapy. *Am Rev Respir Dis* 1982;126:460-62.
- ③ 5. Centers for Disease Control and Prevention. Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. *Morb Mortal Wkly Rep* 2002; 51:214-15; www.cdc.gov/nchstp/tb/

- ③ 6. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986;133:423-30.
- ① 7. Benator D, Bhattacharaya M, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: A randomized clinical trial. *Lancet* 2002;360:528-34.
- ③ 8. Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: Principles of therapy and revised recommendations. *Morb Mortal Wkly Rep* 1998;47: 1-58; www.cdc.gov/nchstp/tb/
- ③ 9. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2000. Atlanta, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2001; www.cdc.gov/nchstp/tb/
- ③ 10. American Thoracic Society/Centers for Disease Control and Prevention/Infection Diseases Society of America. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221-47.
- ① 11. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: Five years of follow-up in the IUAT trial. *Bulletin WHO* 1982;60:555-64.
- ② 12. Snider DE, Caras GJ, et al. Preventive therapy with isoniazid: Cost-effectiveness of different durations of therapy. *JAMA* 1986;255:1579-83.
- ③ 13. Centers for Disease Control and Prevention. Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection *MMWR*. 2003; 52:735-39.
- ① 14. Hong Kong Chest Service, Tuberculosis Research Centre, Madras, and British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis* 1992;145:36-41.
- ① 15. Strang JI, Kakaza HH, et al. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet* 1987;2:1418-22.
- ① 16. Strang JI, Kakaza HH, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet* 1988;2:759-64.
- ① 17. Medical Research Council Working Party on Tuberculosis of the Spine. Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9, or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. *Int Orthop* 1999;23:73-81.

18. Wyser C, Walzl G. Corticosteroids in the treatment of tuberculous pleurisy: A double-blind, placebo-controlled, randomized study. *Chest* 1996;110:333-38.
19. Girgis NI, Farid Z, et al. Dexamethasone adjunctive treatment for tuberculous meningitis. *Pediatr Infect Dis J*. 1991; 10:179-83

FEVER OF UNKNOWN ORIGIN

Definitions, Etiology, and Epidemiology

- Classic criteria of fever of unknown origin (FUO) proposed by Petersdorf and Beeson in 1961¹ are still accepted:
 - Fever $\geq 38.3^{\circ}\text{C}$ (100.9°F) on several different occasions
 - Duration of febrile illness at least 3 weeks (definition may be foreshortened in immunocompromised patients, e.g., neutropenia, HIV, intensive care unit)
 - Uncertain etiology after 1 week of inpatient investigation (or comparable outpatient investigation²)
- Classically divided into four etiological categories in HIV-negative adult patients³
 - Infectious: mortality rate is 8%-22%, most commonly tuberculosis, deep seated intra-abdominal abscess, infective endocarditis, and osteomyelitis
 - Malignant: 5-year mortality rate is $>52\%$, Hodgkin's and non-Hodgkin's lymphoma, leukemia, hepatocellular carcinoma, and renal cell carcinoma
 - Inflammatory: in elderly, temporal arteritis and polyarteritis nodosa (PAN) account for 17% of FUO cases and juvenile rheumatoid arthritis in younger patients
 - Undetermined: the fraction of undiagnosed FUO declined up to the 1950s (with improved diagnos-

tic tools) but has since then steadily increased to about 30%; most of these patients (51%-100%) recover spontaneously

ALPHABETIZED SELECTED ETIOLOGIES OF FUO IN HIV-NEGATIVE, ADULT PATIENTS

Infectious (28%)	Malignant (17%)	Inflammatory (21%)	Miscellaneous (19%)
Amoebic liver abscess	Atrial myxoma	Adult Still's disease	Drug fever
Atypical mycobacteria	Kaposi's sarcoma	Allergic granulomatous angiitis	Environmental toxins
Bacterial endocarditis	Leukemia	Behçet's disease	Factitious fever
Brucellosis	Lymphoma	Granulomatous hepatitis	Familial Mediterranean fever
Cat-scratch disease	Myelodysplastic syndromes	Hypersensitivity vasculitis	Periodic fever
Chronic active hepatitis	Solid tumors	Inflammatory bowel disease	Pulmonary emboli
Cytomegalovirus (CMV)/		Panaortitis	Retroperitoneal hematoma
Ebola virus		Pericarditis	Temperature regulation disorders
Dental abscesses		Reiter's syndrome	
Diskitis		Rheumatoid arthritis	
Epididymitis		Sarcoidosis	
Gonococcal arthritis		Systemic lupus erythematosus	
Herpes simplex encephalitis		Temporal arteritis	
Intra-abdominal abscess		Thrombophlebitis	
Invasive mycoses		Thyroiditis	
Kala azar			
Lyme disease			
Malaria			

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ALPHABETIZED SELECTED ETIOLOGIES OF FUO IN HIV-NEGATIVE, ADULT PATIENTS *(Continued)*

Infectious (28%)	Malignant (17%)	Inflammatory (21%)	Miscellaneous (19%)
Osteomyelitis			
Prostatitis			
Pyelonephritis			
Pyometria			
Q-fever			
Rheumatic Fever			
Rocky Mountain Spotted Fever			
Septic renal calculi			
Sinusitis			
Syphilis			
Tuberculosis			
Typhoid fever			
Whipple's disease			

Pearls of the History and Physical Examination

History

- Keeping “fever journals” for the determination of classic fever patterns (e.g., relapsing-sustained, temperature-pulse disparity, intermittent) has demonstrated low specificity in the diagnosis of FUO, although in rare cases they may prove useful (Pel-Ebstein fever, drug fever, malaria)⁴
- Travel history
- Exposure to pets, livestock, or unpasteurized dairy products
- History of immunosuppression (malignancy, HIV, diabetes, glucocorticoid use)

- Symptoms of autoimmune/inflammatory disease (arthralgias, jaw claudication, hematochezia)
- Recent surgery or trauma (particularly involving foreign bodies)
- Thorough medication history, including over-the-counter drugs (diet pills, antihistamines, decongestants), alternative medicines or supplements (see following table)
- Substance use (particularly IV)
- Gynecological/sexual history
- Known familial disorders
- Tooth pain or recent dental procedures
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or glucocorticoids, all of which may attenuate fever

Physical Examination

- Serial examinations often essential
- Careful evaluation of skin, lymph nodes, and mucous membranes
- Heart murmurs and/or stigmata of endocarditis

ALPHABETIZED MEDICATIONS COMMONLY ASSOCIATED WITH DRUG-INDUCED FEVER

Hypersensitivity ^{5,6}	Altered Thermoregulation ^{6,7}	Parenteral Infusion Reactions
Abacavir	Exogenous thyroid hormone ⁸	Amphotericin B
Allopurinol		Bleomycin
Anticonvulsants (carbamazepine, phenytoin)	Anticholinergics ^{7,9} • Anti-parkinsonian agents	Immunologics (interferon, intravenous immunoglobulins)
Barbituates	• Atropine and belladonna alkaloids (antispasmodics, antidiarrheals)	Pentazocine
Beta-lactams		Paraldehyde
Captopril		
Clofibrate	• Butyrophenone tranquilizers	
Erythromycin		

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ALPHABETIZED MEDICATIONS COMMONLY ASSOCIATED WITH DRUG-INDUCED FEVER (*Continued*)

Hypersensitivity ^{5,6}	Altered Thermoregulation ^{6,7}	Parenteral Infusion Reactions
H ₂ -antagonists	• Phenothiazines	
Heparin	• Tricyclic antidepressants	
Hydralazine	Sympathomimetics ^{7,8}	
Iodides	• Amphetamines	
Isoniazid	• Cocaine	
Meperidine	• Decongestants	
Methyldopa	• MDMA ("Ecstasy")	
Minocycline	• Methylphenidate	
Nifedipine	• Herbal supplements (Guarana, Ma Huang, Gotu Kola, ephedrine)	
Nitrofurantoin		
NSAIDs and salicylates		
Procainamide		
Quinidine		
Rifampin		
Sulfonamides and other sulfurous compounds (e.g., diuretics, celecoxib)		

- Abdominal masses or organomegaly
- Thorough gynecological examination in women
- Prostate examination in men (unless neutropenic)
- Assess thyroid for tenderness (can be subtle) or enlargement
- Temporal artery tenderness in patients past fifth decade

Diagnostic Studies and Laboratory Values

Blood Tests³

- Blood cultures^{10,11}
 - Disinfectant should be allowed to dry before blood collection

- Three sets of cultures should be drawn from different sites over several hours
- For fastidious organisms or *Mycobacterium avium* complex, laboratory may require notification to hold specimen for extended period
- Consider fungal isolates if routine culture results negative
- Serial blood cultures unlikely to increase yield and increase likelihood of obtaining a contaminated specimen
- Complete blood count with differential (peripheral smear should be reviewed by a hematopathologist)
- Metabolic panel, liver enzymes, lactate dehydrogenase
- Urinalysis with microscopy, urine culture, and sensitivities
- Rheumatoid factor, antinuclear antibody, HIV antibody testing, heterophile and/or CMV IgM antibody testing in adolescents and young adults, Q-fever serology (if at risk for zoonotic or laboratory exposure)
- Specialized tests, such as autoimmune panels, phosphocreatine kinase, thyroid-stimulating hormone, rapid plasma reagin, viral or hepatitis serologies, cerebrospinal fluid analysis, endemic fungal antigens, stool studies, etc., should be based on history or suggestive signs and symptoms
- Purified protein derivative test for active tuberculosis has a 25% false-negative rate¹²
- Erythrocyte sedimentation rate (ESR) and C-reactive protein
 - No data to support or refute the routine use of these tests in FUO
 - Certain conditions, such as nephrotic syndrome, multiple myeloma, drug hypersensitivity reactions, and thrombophlebitis, may elicit high ESR in the absence of infection
 - However, few conditions cause extreme elevations of ESR (>100 mm/h): metastatic malignancy,

collagen vascular diseases, and infections such as infective endocarditis and osteomyelitis¹³

- Normal ESR does not always exclude inflammatory diseases such as temporal arteritis or polyarteritis nodosa³

Radiographic Imaging

- Chest x-ray
- Abdominal computed tomography: for abscess or malignancy has a high diagnostic yield (19%) and has significantly reduced the need for invasive diagnostic studies in the workup of FUO; most published guidelines recommend this early in the routine evaluation of FUO^{3,14}
- Any prosthetic device and its surrounding tissues should be assessed, irrespective of how long it has been in place¹⁵
- Nuclear imaging
 - Evidence exists in support of nuclear imaging studies in patients whose diagnoses remain unclear after routine work-up is performed
 - Technetium-based scans are the only modality reliably shown to have sufficient specificity (93%-94%) to be diagnostically useful; gallium- and indium-based scans are not recommended³
- Transthoracic echocardiograms are significantly inferior to transesophageal for visualizing vegetations and myocardial abscesses⁸
- Temporal artery biopsy should be considered in elderly patients with FUO (although sensitivity in patients without headache, temporal artery tenderness, and/or jaw claudication is only 10%-15% and 4.4% in patients with isolated PAN)
- The diagnostic yield of liver biopsy is 14%-17%, with low morbidity and mortality rates
- Three case series report deep vein thrombosis as the etiology of FUO in 2%-6% of patients; thus,

lower extremity Doppler studies may be useful for patients at risk³

Guide to Acute Management

- Usefulness of empiric therapy (antibiotics, corticosteroids, antituberculous agents) has not been studied; majority consensus is to avoid this approach because it obscures or confuse the diagnosis
- As most patients with nonestablished diagnoses after extensive work-up recover spontaneously, close observation and follow-up without intervention is a reasonable and safe strategy in these cases¹⁶



Patient Care Warning

- Pursue infectious avenues aggressively due to relatively higher mortality risk

References

- ② 1. Petersdorf RG, Beeson P. Fever of unexplained origin: Report on 100 cases. *Medicine* 1961;40:1-30.
- ③ 2. Petersdorf RG. Fever of unknown origin: An old friend revisited. *Arch Intern Med* 1992;152:21-22.
- ① 3. Mourad O, Palda V, Detsky A. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med* 2003;163:545-51.
- ③ 4. Hirschmann JV. Fever of unknown origin in adults. *Clin Infect Dis* 1997;24:291.
- ③ 5. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005;209:123-29.
- ③ 6. Cuddy ML. The effects of drugs on thermoregulation. *AACN Clin Issues* 2004;15:238-53.
- ③ 7. Chan TC, Evans SD, Clark RF. Drug-induced hyperthermia. *Crit Care Clin* 1997;13:785-808.
- ③ 8. Lewander WJ, Lacouture PG, Silva JE, et al. Acute thyroxine ingestion in pediatric patients. *Pediatrics* 1989;84:262-65.

- ③ 9. Halloran LL, Bernard DW. Management of drug-induced hyperthermia. *Curr Opin Pediatr* 2004;16:211-15.
- ① 10. Little JR, Murray PR, Traynor PS, et al. A randomized trial of povidone-iodine compared with iodine tincture for venipuncture site disinfection: Effects on rates of blood culture contamination. *Am J Med* 1999;107:119-25.
- ② 11. Norberg A, Christopher NC, Ramundo ML, et al. Contamination rates of blood cultures obtained by dedicated phlebotomy vs. intravenous catheter. *JAMA* 2003;289:726.
- ③ 12. Morey SS. ATS adopts diagnostic standards for tuberculosis. *Am Fam Physician* 2001;63:979-81.
- ② 13. Fincher RM, Page MI. Clinical significance of extreme elevation of the erythrocyte sedimentation rate. *Arch Intern Med* 1986;146:1581-83.
- ③ 14. Roth AR, Basello GM. Approach to the adult patient with fever of unknown origin. *Am Fam Physician* 2003;68:2223-28.
- ③ 15. Amin K, Kauffman CA. Fever of unknown origin. *Postgrad Med* 2003;114: 69-75.
- ② 16. Knockaert DC, Dujardin KS, Bobbaers HJ. Long-term follow-up of patients with undiagnosed fever of unknown origin. *Arch Intern Med* 1996;156:618.

POSTEXPOSURE PROPHYLAXIS OF HIV INFECTION

Definitions, Etiology and Epidemiology

- Postexposure prophylaxis (PEP) of HIV seroconversion after occupational exposure (e.g., needle-stick injury)
- PEP of HIV seroconversion after high-risk sexual contact (e.g., rape) or needle sharing

Occupational Exposure

- Overall risk of seroconversion is very low
 - 0.33% from needle-stick injury
 - 0.09% from mucosal exposure (e.g., conjunctiva)
 - 0% from intact skin exposure¹
- Significant risk factors
 - Hollow-bore needle

- Deep-tissue inoculation
- Visible blood on device from source patient
- Exposure during attempt at intravascular access
- High plasma viral load of source patient²

High-Risk Sexual Contact

- Risk varies with mode of sexual contact, viral load of source partner, presence of concomitant sexually transmitted diseases, etc.
- Oral sex is a valid means of HIV transmission
- A negative HIV antibody test in source contact can be misleading; plasma viral load and infectivity can be extremely high during acute seroconversion when conventional antibody assays may still be negative

Pearls of the History and Physical Examination

- Time and date of exposure
- HIV serostatus of source, if known
- Hepatitis B and C serostatus of source, if known
- If serostatus of source known, details of previous or present antiretroviral therapy and most recent viral load, as these data may assist in choice of PEP regimen
- Method of exposure (type of procedure, exact details of injury, whether patient or source blood was visible, etc.)

Diagnostic Studies and Laboratory Values

- Baseline HIV and hepatitis B and C antibody testing should be performed in both the patient and the source contact; the absence of a negative baseline antibody test in the patient may preclude options for Workers Compensation or other employee benefits in the event of seroconversion

- If source is known to be HIV-positive, may consider performing plasma viral load assay $\pm$ resistance testing on source to help guide choice of PEP regimen
- Know the consent laws for your state; in many states consent requirements are waived in the setting of occupational exposure; however, most states still require that a form be completed for the chart

Guide to Acute Management

Occupational Exposure

- Inoculum sites exposed to potentially infectious fluids (blood, semen, vaginal secretions, and cerebrospinal, synovial, peritoneal, pleural, pericardial, and amniotic fluids) should be cleansed vigorously with soap and water; mucous membranes should be irrigated thoroughly with saline or water.
- PEP Guidelines³
 - Presently a regimen containing AZT (zidovudine) is preferred, based on one Centers of Disease Control (CDC)–sponsored case control study that suggested an odds ratio of 0.19 for HIV transmission when AZT was used for PEP in the health-care setting
 - AZT remains the only drug to have been studied for PEP
 - In 2001 guidelines were revised to include 3TC (lamivudine) and, in some cases, combination therapy with AZT 3TC and a protease inhibitor based on the observation of greater antiviral potency with the combination therapies
- Do not delay induction of PEP, if indicated; delay definitely decreases efficacy
- Duration of treatment is 4 weeks in all regimens
- AZT and 3TC are available as the combination tablet Combivir, which is administered bid

- If source is suspected to have resistant virus (e.g., has received prior antiretroviral therapy), expert consultation is indicated for choice of PEP
- If source is determined to be HIV-negative, treatment should be discontinued
- Serology should be reassessed at 6 weeks, 12 weeks, and 6 months following exposure
- Complete blood test, liver function tests, and plasma creatinine should also be measured at baseline and after 2 weeks of PEP to monitor for drug toxicity
- Women of childbearing age who are exposed should be tested for pregnancy and referred for expert consultation if positive
 - However, pregnancy itself is not a contraindication to prophylaxis
- Patient reassurance, education, and adherence are paramount
 - Patients are more likely to comply with treatment if they know what to expect
 - Explain odds of seroconversion (including hepatitis B and C), PEP options, drug side effects, symptoms of acute retroviral syndrome (see section titled Acute Retroviral Syndrome) and importance of using protection with sexual partners until seroconversion has been definitively ruled out
 - Stress rigorous compliance with regimen and importance of follow-up with physicians or Occupational Health
- Hepatitis B and C are much more readily transmitted during occupational exposures than HIV (see Morb Mortal Wkly Rep 2001;50:1-42 for further recommendations)

High-Risk Sexual Contact

- No definitive data exist as to efficacy of prophylaxis in this situation

Exposure Type	HIV-Positive Class I α	HIV-Positive Class II β	Source HIV Status Unknown	Source Unknown	Source HIV-Negative
Percutaneous, less severe*	2-drug	3-drug	2-drug or none	2-drug or none	None
Percutaneous, more severe**	3-drug	3-drug	2-drug or none	2-drug or none	None
Mucous membrane, small volume $\dagger$	2-drug	2-drug	2-drug or none	2-drug or none	None
Mucous membrane, large volume $\dagger\dagger$	2-drug	3-drug	2-drug or none	2-drug or none	None

Bold items represent recommended regimens for most circumstances; nonbold items represent options for consideration based on individualized assessment of exposure risk

*Less severe (e.g., solid needle or superficial injury)

**More severe (e.g., large or hollow-bore needle, visible blood on device, deep puncture, or intravascular access)

$\dagger$ Small volume (i.e., a few drops)

$\dagger\dagger$ Large volume (i.e., blood splash)

α HIV-positive, class I: asymptomatic infection or documented low plasma viral load (<1500 copies/mL)

β HIV-positive, class II: symptomatic infection, AIDS, acute seroconversion, known high plasma viral load

2-drug regimen: AZT (zidovudine), 200 mg po tid or 300 mg po bid; 3TC (lamivudine) 150 mg po bid

3-drug regimen: AZT/3TC plus a protease inhibitor, such as nelfinavir 750 mg po tid or 1250 mg po bid; indinavir 800 mg po q8h on an empty stomach; lopinavir-ritonavir 3 tablets po bid

- It may be reasonable to assume that methods used for occupational exposure prophylaxis may have potential utility in other exposure scenarios
- Current CDC guidelines recommend PEP for high-risk sexual contacts
- Given that the source partner's HIV status frequently cannot be determined and the fact that there is typically a greater delay between time of exposure and initiation of treatment, the decision to initiate prophylaxis must be negotiated extensively with the patient
- Note that the patient may be denied insurance coverage for this indication
- Guidelines for choice of PEP regimen are similar to those for occupational exposure
 - Most experts recommend that prophylaxis be considered only within 72 hours of exposure
 - A two-drug regimen is suggested for most cases, with the addition of a preliminary incubation for source cases with:
 - Viral loads >50,000 copies/mL
 - Symptomatic HIV infection
 - Acute seroconversion
 - Prior nucleoside exposure (i.e., AZT, 3TC, ddI, D4T, ddC, FTC, abacavir, tenofavir)
 - If source case is known to have achieved virological control (i.e., an undetectable viral load) on a particular regimen, it may be reasonable to use the same regimen for prophylaxis⁴⁻⁶
 - Baseline and follow-up testing as above



Patient Care Warnings

- Do not delay PEP

References

- ② 1. Henderson DK, Fahey BJ, Willy M, et al. Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures: A prospective evaluation. *Ann Intern Med* 1990;113:740.
- ② 2. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *N Engl J Med* 1997;337:1485.
- ③ 3. CDC. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *Morb Mortal Wkly Rep* 2001;50.
- ③ 4. Katz MH, Gerberding JL. The care of persons with recent sexual exposure to HIV. *Ann Intern Med* 1998;128:306.
- ③ 5. Bamberger JD, Waldo CR, Gerberding JL, et al. Postexposure prophylaxis for human immunodeficiency virus (HIV) infection following sexual assault. *Am J Med* 1999;106:323.
- ② 6. Kahn JO, Martin JN, Roland ME, et al. Feasibility of postexposure prophylaxis (PEP) against human immunodeficiency virus infection after sexual or injection drug use exposure: The San Francisco PEP Study. *J Infect Dis* 2001;183:707.

TICK-BORNE ILLNESSES

Definition and Etiology¹

- Most common of the zoonoses or vector-borne diseases in the United States; ticks are second only to mosquitoes as vectors of disease worldwide.
- Different ticks cause different diseases; representative sample of diseases seen in parts of the United States are discussed subsequently.
- Visible ticks should be removed by grasping the anterior aspect (the head) and pulling out completely; crushing or puncturing the body of the tick should be avoided, as this can actually facilitate the release of organisms

Lyme Disease¹⁻³

- Causative agent is a spirochete *Borrelia burgdorferi*; the tick vector is *Ixodes* spp.

- Transmitted from the tick in the nymph stage, with peak transmission in May through July
- The nymph is usually only barely visible to the naked eye; visible tick bites are less likely to result in Lyme disease
- Endemic to the northeastern, mid-Atlantic, and mid-western states

Clinical Manifestations

- Stage 1: early clinical manifestation
 - Erythema migrans (EM): 3-32 days after tick bite
 - Lesions are typically warm but not painful and are located at the site of tick attachment
- Stage 2: represents disseminated infection
 - Skin manifestations: multiple lesions that differ slightly from those of EM (less migration, no indurated center, not associated with tick attachment sites)
 - Generalized malaise, regional lymphadenopathy, musculoskeletal pain, meningeal irritation, fatigue and lethargy
 - Frequently occurs sequentially and separately
 - Cerebrospinal fluid (CSF) in those involved shows lymphocytic pleocytosis, a high protein level, and a normal glucose level
 - Isolated seventh-nerve palsy may occur
 - Cardiac manifestations occur in a minority, most commonly as atriovenous block
- Stage 3: persistent infection
 - Can be divided into musculoskeletal and neurological manifestations
 - Generally occurs only in untreated patients, although 1%-2% of Lyme disease patients can have autoimmune-mediated complications despite absence of evidence of persistent spirochetes after treatment

Diagnosis

- Clinical or confirmed by laboratory testing²
- In known exposure, presence of EM is sufficient for diagnosis
- In patients with intermediate probability, a two-step method (enzyme-linked immunosorbent assay followed by Western blot) is recommended
- In patients with low probability, no further testing is recommended
- No laboratory tests are truly definitive; empiric therapy often given, when in doubt

Treatment³

- Early and disseminated stages respond to doxycycline or amoxicillin for 30 days
 - Cefuroxime, ceftriaxone, and macrolide antibiotics have been suggested for those intolerant of doxycycline and amoxicillin
- Complete heart block: parenteral antibiotics (ceftriaxone 2 g intravenous [IV] daily or penicillin G 20 million U over 24 hours for 30 days) and, if necessary, temporary pacing
- Lyme arthritis may require treatment as long as 60 days
- Neurological disease: IV ceftriaxone or penicillin G as for complete heart block (see preceding)
- For known tick bites in endemic areas, some experts recommend empiric therapy as for early Lyme disease; visible ticks usually cause diseases other than Lyme disease
- After appropriate therapy, residual neurological symptoms and arthritis are generally mediated by autoimmunity; no evidence of persistence of spirochetes in patients adequately treated; prolonged course of antibiotics are not indicated; persistent complaints need to be treated symptomatically (nonsteroidal anti-inflammatory drugs, etc.) and psychiatric comorbidities need to be addressed

Rocky Mountain Spotted Fever^{1,4}

- Causative agent is an obligate intracellular parasite *Rickettsia rickettsii*, vector *Dermacentor* spp.
- Most lethal of the tick-borne infections, with a mortality rate approaching 25%
- Most cases are reported from rural states; first case identified in Idaho, although not particularly prevalent in the Rocky Mountains at this time
- Currently, most cases reported in Montana, South Dakota, Missouri, Oklahoma, North Carolina, South Carolina, and Georgia

Clinical Manifestations

- Derive from the damage *Rickettsia* causes to the endothelium in skin, heart, lungs, brain, gastrointestinal (GI) tract, and other tissues
- Clinical triad: rash, fever, and headache are classic (present in less than half of cases)
- Incubation time is typically 7 days
- GI manifestations are common, and Rocky Mountain spotted fever is often initially misdiagnosed as gastroenteritis
- Rash classically appears 3-5 days after onset of fever; may be macular rather than petechial early and usually begins on the wrists and ankles (although this is variable); classically on palms and soles
- Headache is typically severe, and neurological complications portend a bad outcome
- CSF findings are quite protean, with neutrophilic or lymphocytic pleocytosis, elevated protein with normal glucose being the most common
- Leukopenia, hyponatremia, elevated lactate dehydrogenase, and prerenal azotemia may be seen
- Death classically occurs in 8-15 days after onset of symptoms but may occur more rapidly in fulminant Rocky Mountain spotted fever, especially in patients with G-6PD deficiency

Diagnosis

- Made clinically; as significant morbidity and mortality can be avoided with early treatment, antibiotics should not be held to await a test result
- Immunofluorescence assays (IFAs) can be used to detect IgG and IgM⁵

Treatment

- Doxycycline for 7-10 days and may be administered orally in patients not requiring hospitalization
- Optimal duration has not been studied prospectively⁵

Other Tick-Borne Infections

Tularemia⁶

- Often contracted through tick bites but may be contracted through direct exposure to rodents (classically rabbits) or inhaled aerosols
- *Francisella tularensis* is a facultative intracellular gram-negative coccobacillus
- A primary skin ulcer or pulmonary symptoms may suggest portal of entry
- Incubation is 3-5 days, although may be longer
- Clinical manifestations can vary:
 - High fevers, malaise, and pulmonary symptoms are common
 - Regional lymphadenopathy may be seen in conjunction with a skin ulcer (ulceroglandular tularemia), although the primary ulcer may not be noticed by the patient and only seen on physical examination
- Diagnosis: clinical and serologic (IgG and IgM antibodies); treatment should not be withheld pending serological confirmation; diagnosis often delayed in nonendemic areas
- Treatment: streptomycin, although gentamicin is an acceptable alternative; tetracyclines are bacteriostatic

for tularemia, and relapse rates are high; expert consultation recommended in areas of low endemicity as not all physicians are experienced with this disease

Babesiosis

- Newly recognized tick-borne infection caused by intracellular protozoa of *Babesia*; four species have been found to be human pathogens
- Ixodes ticks, such as those in Lyme disease, are the responsible vector, with the white-footed mouse occurring as the mammalian reservoir; coinfection with *Borrelia burgdorferi* is not uncommon
- Endemic in wooded areas, such as the northeastern United States, Minnesota, and Wisconsin, and occurs in the summer months
- Babesiosis has been acquired through blood transfusions
- Risk of serious disease increases in patients older than 50, people with splenectomy, and people with cell-mediated immunodeficiency (including HIV); concurrent Lyme disease also causes more severe presentations
- Clinical manifestations
 - Range from fulminant disease with an outcome of death or prolonged recovery, severe disease, mild disease, and subclinical disease (detected by retrospective serologies); most cases are subclinical
 - Tick bites are not always reported, and disease incubation ranges 1-6 weeks
 - Nonspecific febrile illness with chills, sweats, malaise, and headaches being reported
 - Fulminant and severe disease is complicated by respiratory and multisystem organ failure with disseminated intravascular coagulation
 - Parasitemia may persist, and previous diagnosis of babesiosis is a contraindication to blood product donation

- As the disease is characterized by invasion and lysis of red blood cells, hemolytic anemia and thrombocytopenia are seen
- Diagnosis
 - Made by demonstration of the organism on blood smear
 - Polymerase chain reaction (PCR) or serological tests may confirm the diagnosis
 - Immunofluorescence assay titer of 1:1024 or greater is suggestive of active disease, with the titer falling off over 1 year
 - In suspected but unproven disease, a patient's blood may be injected into laboratory hamsters, with the appearance of organisms in the hamster's blood in 2-4 weeks
- Treatment
 - Most patients recover without treatment; for severe disease:
 - Clindamycin and quinine for 7-10 days, but not tolerated well
 - Azithromycin plus atovaquone have been shown to be equivalent to and better tolerated than first-line therapy⁷
 - In severe babesiosis, exchange transfusion may be used

Ehrlichiosis⁸

- Another recently recognized tick-borne infection
- Sometimes referred to as "spotless Rocky Mountain Spotted Fever", although Rocky Mountain spotted fever may present without "spots" (or rash); some cases of ehrlichiosis do present with rash
- Represents a group of diseases caused by *Ehrlichia* spp., small gram-negative rods that infect phagocytic host cells
- Most patients give a history of tick exposure in the month before disease onset

- Distribution of cases roughly corresponds to the distribution of the “Lone Star tick”
- Mammalian reservoir includes the white-footed mouse and the white-tailed deer
- Clinical manifestations:
 - Nonspecific febrile disease also characterized by headache
 - Rash is not a prominent feature, although it can occur in 10%-30% of cases
 - Fulminant disease is rare, and the fatality rate is estimated at < 1%, but risk may be increased with concomitant disease and failure to initiate antibiotic therapy
- Diagnosis
 - Made clinically with the support of appropriate laboratory tests
 - As the pathogen affects hematopoietic cell lines, it is not uncommon to see leukopenia with thrombocytopenia
 - Neutrophil morulae may be seen by experienced examination of the peripheral blood smear; diagnosis can be divided into possible, probable, and confirmed cases as follows:
 - History of tick exposure, febrile illness, and nonspecific evaluation represent possible disease
 - Above and either a single IFA titer >80, a positive PCR result, or morulae seen on blood smear represents probable disease
 - A fourfold increase in IFA titer, a positive PCR result, and morulae on blood smear, or a positive blood culture confirms disease
- Treatment
 - 14-day course of doxycycline or tetracycline is effective
 - Prognosis is usually remarkable for complete resolution within 2 months, even without appropriate therapy; occasionally, neurological sequelae have been reported



Patient Care Warnings

- A clear history of a tick bite can be very helpful, but its absence should not exclude the diagnosis of a tick-borne infection
- Tick-borne infections should be considered in all FUO, especially in spring and summer months

References

- ③ 1. Mandell G. Principles and Practice of Infectious Diseases, 5th ed, Churchill Livingstone, 2000:2504-13.
- ② 2. Tugwell P, Dennis DT, Weinstein A, et al. Laboratory evaluation in the diagnosis of Lyme disease. *Ann Intern Med* 1997;127:1109.
- ③ 3. Wormser G, Nadelman R, Dattwyler R, et al. Practice guidelines for the treatment of Lyme disease. *Clin Infect Dis* 2000;31:1-14.
- ③ 4. Krause PJ. Babesiosis. *Med Clin North Am* 2002;86:361-73.
- ③ 5. Sexton DJ, Kaye KS. Rocky Mountain spotted fever. *Med Clin North Am* 2002;86:351-60.
- ③ 6. Tarvnik A, Berglund L. Tularemia. *Eur Respir J* 2003;21:361-73.
- ① 7. Krause PJ, Lepore T, Sikand VK, et al. Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000;343:1454-58.
- ③ 8. Bakken J, Dumler JS. Human granulocytic ehrlichiosis. *Clin Infect Dis* 2000;31:554-60.

HEMATOLOGY AND ONCOLOGY

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Definition, Etiology, and Epidemiology

- Acute lymphoblastic leukemia (ALL) results from abnormal clonal proliferation of a lymphoid hematopoietic progenitor cell in peripheral blood, bone marrow, or other organs
- Etiology remains obscure in most cases; strongest associations exist with genetic, Epstein-Barr virus (EBV), and HIV (in patients with mature B-cell ALL)
- Approximately 5000 patients annually are diagnosed with ALL in the United States
- Most common: childhood leukemia (25% of all childhood malignancies, 80% of all childhood leukemias)
- Represents only 20% of all adult leukemia
- Has bimodal distribution
 - Incidence of 4-5 per 100,000 between ages 2-4 years
 - Incidence of 1 per 100,000 in patients >50 years

Pearls of the History and Physical Examination

- Symptoms arise from the proliferation of leukemic cells in bone marrow, peripheral blood, and extramedullary sites (central nervous system [CNS])
 - Bone marrow: bleeding, bruising, fever, and infection

- Peripheral blood: fatigue, dyspnea/hypoxia, and arthralgias secondary to leukostasis
- CNS: headache and/or cranial nerve palsy

Physical Examination

- May reveal pallor, ecchymoses, or petechiae
- Hepatosplenomegaly and lymphadenopathy are infrequent and rarely symptomatic
- Cranial nerve palsies are more commonly observed in mature B-cell ALL
 - These patients often present with cranial nerve deficiencies (especially III, IV, VI, and VII), leading to double vision, abnormal ocular movements, facial dysesthesia, and facial droop

Diagnostic Studies and Laboratory Values

- Complete blood count, coagulation studies (looking for evidence of disseminated intravascular coagulation), serum chemistries (looking for evidence of tumor lysis syndrome)
- Consider lumbar puncture to look for CNS involvement
- Evaluation of the peripheral blood smear should reveal circulating blasts in the acute phase
- Chest x-ray may reveal a mediastinal mass (most commonly seen in T-cell ALL)
- Bone marrow biopsy usually reveals $>30\%$ blasts: classification based on morphology and immunophenotype of the cells
 - French-American-British (FAB) Classification: types L1, L2, and L3 are based on cell size, amount of cytoplasm, prominence of nucleoli, degree of cytoplasmic basophilia, and vacuolation
 - Immunophenotype: based on flow cytometry
 - Precursor B-cell
 - Mature B-cell
 - T-cell

Guide to Acute Management

- Treatment of ALL consists of four steps:
 - Induction therapy¹⁻³
 - Vincristine + corticosteroids (usually prednisone) achieve complete remission rates of 40%-65%, but median duration of disease remission is only 3-7 months
 - Vincristine + corticosteroids + anthracycline have increased complete remission rate to 70%-90% and median duration to 18 months
 - Granulocyte colony-stimulating factor (G-CSF) can be added to shorten the period of neutropenia, but G-CSF has not been shown to prolong the disease-free or overall survival time
 - Adding other agents, such as cyclophosphamide, cytarabine, methotrexate, and asparaginase, has been tried, but their roles remain unclear
 - Consolidation therapy
 - Consolidation therapy may include a modified induction therapy, rotational consolidation program, or stem cell transplant; current therapy is based on the subtype of ALL
 - CNS prophylaxis^{4,5}
 - CNS disease is rare at diagnosis but may be diagnosed in up to 75% of patients at 1 year (in the absence of CNS-directed therapy)
 - CNS prophylaxis includes intrathecal chemotherapy (methotrexate, ara-C, steroids), high-dose systemic chemotherapy (methotrexate, ara-C, L-asparaginase), and craniospinal irradiation
 - Maintenance therapy⁶
 - Standard therapy consists of daily doses of 6-mercaptopurine, weekly doses of methotrexate, and monthly pulses of vincristine + prednisone given over 2-3 years
 - Extension of maintenance regimens beyond 3 years has not shown additional benefits

Complications at Acute Presentation

- Leukostasis: secondary to high leukemic cell burden; may require emergent plasmapheresis
- Tumor lysis syndrome: occurs secondary to the lysis of intracellular products during therapy, resulting in the development of hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and lactic acidosis; can cause oliguria and acute renal failure (secondary to precipitation of uric acid and calcium phosphate crystals in the renal tubules)
- Bone marrow suppression: results in anemia, thrombocytopenia, and neutropenia and should be treated accordingly
- Bone marrow transplant: these patients should be monitored closely for complications of graft-versus-host disease and opportunistic infections (*Pneumocystis carinii* pneumonia, cytomegalovirus, herpes simplex virus)

Prognosis

- Poor prognostic factors include age >50 years, poor performance status, male > female, black, time to complete remission >4 weeks, leukocytosis ($>30 \times 10^9$ cell/L (B lineage), $>100 \times 10^9$ cell/L (T lineage), and translocation t(9;22), t(4;11)



Patient Care Warnings

- When treating patients with ALL, be aware of the risk for tumor lysis syndrome and consider initiating allopurinol prophylaxis
- Symptoms of leukostasis may require emergent plasmapheresis

References

- ③ 1. Stryckmans P, Debusscher L. Chemotherapy of adult acute lymphoblastic leukemia. *Bailliers Clin Haematol* 1991;4:115-30.
- ② 2. Kantarjian HM, O'Brien S, Smith T, et al. Acute lymphoblastic leukaemia in the elderly. *Br J Haematol* 1994;88:94-100.
- ② 3. Kantarjian HM, Walters RS, Keating MJ, et al. Experience with vincristine, doxorubicin, and dexamethasone chemotherapy in adults with refractory acute lymphocytic leukemia. *Cancer* 1989;64:16-22.
- ② 4. Cortes J, O'Brien SM, Pierce S, et al. The value of high-dose systemic chemotherapy and intrathecal therapy for CNS prophylaxis in different groups of ALL. *Cancer* 1995;86:2091-97.
- ③ 5. Bleyer WA, Poplack DG. Prophylaxis and treatment of leukemia in the CNS and other sanctuaries. *Semin Oncol* 1985;12:131-48.
- ① 6. Cuttner J, Mick R, Budman DR, et al. Phase III trial of brief intensive treatment of ALL comparing danorubicin and mitoxantrone. *Leukemia* 1991;5:425-31.

ACUTE MYELOGENOUS LEUKEMIA (AML)

Definition, Etiology, and Epidemiology

- Acute myelogenous leukemia (AML) is a malignant disorder of the bone marrow in which hematopoietic cells are arrested at an early stage of development, resulting in >30% blasts in the blood and/or bone marrow
- Pathophysiology usually involves chromosomal translocations that result in the abnormal activation of genes
- AML occurs in all age groups, with the median age of onset being 60 years

Pearls of the History and Physical Examination

- World Health Organization (WHO) classification scheme based on treatment outcome and cytogenetic abnormalities
 - AML with recurrent cytogenetic abnormalities

- Favorable cytogenetics include: t(15:17), t(8:21); inversion chromosome 16(1)
- AML with multiple-lineage dysplasia: usually in elderly following myelodysplastic syndrome
- Therapy-related AML: secondary to chemotherapy
- AML not otherwise categorized: based on degree of differentiation from M0-M7
 - M3: acute promyelocytic leukemia (APL) associated with disseminated intravascular coagulation (DIC)
 - M5: monoblastic leukemia that tends to infiltrate extramedullary tissue resulting in gingival hyperplasia in 50% of patients due to infiltration by blasts, leukemia cutis with multiple nontender rose-colored papules, hypokalemia and hypomagnesemia secondary to proximal tubule injury by monoblast-derived lysosyme
- Symptoms in AML are the consequence of bone marrow failure, resulting in varying degrees of:
 - Neutropenia: fever, infection; risk highest in patients with a neutrophil count <500
 - Thrombocytopenia: bleeding gums, ecchymoses, life-threatening bleeding
 - Anemia: fatigue, exertional dyspnea, orthopnea, angina
- Leukostasis may occur when blast count exceeds 100,000; associated with respiratory compromise or central nervous system (CNS) complaints
- Spurious hypoxemia may occur with high blast counts

Diagnostic Studies and Laboratory Values

Blood Tests

- Complete blood count: may observe varying amounts of anemia and thrombocytopenia; high, normal, or low white blood cell (WBC) count
 - Circulating blasts are usually seen
 - Schistocytes if DIC is present

- Serum chemistries
 - Usually elevated lactate dehydrogenase (LDH) and uric acid levels
 - Monitor liver function tests and serum creatinine with treatment
 - Spurious hyperkalemia may occur with high blast counts
- Coagulation studies and fibrinogen and D-dimer tests to evaluate for DIC

Bone Marrow Aspiration

- AML patients have >30% blasts in the marrow
- Allows for morphological characterization into subtypes M0-M7

Other Studies

- Cytogenetic studies are necessary for WHO classification and carry prognostic information¹
- Immunophenotyping by flow cytometry as an adjunct to cytogenetics
- Multiple gated acquisition scan evaluates pretreatment cardiac function prior to use of potentially cardiotoxic chemotherapeutic agents

Guide to Acute Management

- Except for APL, treatment of AML involves:
 - Induction
 - “3 and 7”: 3 days of anthracycline and 7 days of ara-C
 - Approximately 50% of patients achieve remission after one course
 - Consolidation: in younger patients, bone marrow transplantation (BMT) versus chemotherapy may be considered²
 - Patients with favorable cytogenetics or those older than 60 years should be offered high-dose ara-C for consolidation

- Patients with unfavorable cytogenetics should be offered BMT
- Monitor cardiac, hepatic, and renal function during induction
- APL is associated with t(15:17) and retinoic acid receptor rearrangement
- APL responds well to treatment with all-trans-retinoic acid (ATRA) and chemotherapy, with reports of remission in more than 90% of patients

Monitoring With Therapy

- Patients usually require supportive care with irradiated blood products for anemia, thrombocytopenia, and neutropenia
- Broad-spectrum antibiotics such as cefepime should be given to all febrile patients
- Tumor lysis syndrome
 - Predisposing factors: high WBC count, hyperuricemia, high LDH level, impaired renal function, sepsis, dehydration
- ATRA syndrome results from ATRA-induced differentiation of blasts into mature cells, causing fever, weight gain, dyspnea, lung infiltrates, pleural or pericardial effusions, hypotension, and renal failure
 - Treat with steroids and cytoreduction
- Leukostasis syndrome: acute dyspnea with pneumonialike symptoms, headache, strokelike syndrome
 - Treat with leukapheresis, chemotherapy, and/or CNS radiation



Patient Care Warnings

- Monitor for tumor lysis
- Symptoms of leukostasis can occur, especially when blast counts rise over 100,000

References

- ② 1. Leith CP, Kopecky KJ, Godwin J, et al. Acute myeloid leukemia in the elderly: Assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct response to standard chemotherapy: A Southwest Oncology Group Study. *Blood* 1997;89:3323.
- ① 2. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. *N Engl J Med* 1995;332:217.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Definition, Etiology, and Epidemiology¹

- One of the chronic lymphoproliferative disorders characterized by an accumulation of functionally incompetent, monoclonal lymphocytes
- Most common leukemia of Western world
 - >40% of all leukemias in patients older than 65 years
 - Incidence 3 per 100,000
- Median age at diagnosis 65-70 years
 - Extremely rare below age 30 years
- Male predominance 2:1

Staging

RAI CLASSIFICATION²

Stage	Characteristics	Median Survival (months)
0	Bone marrow and peripheral lymphocytosis	150
I	+ Lymphadenopathy	101
II	+ Splenomegaly or hepatomegaly	71
III	+ Anemia	19
IV	+ Thrombocytopenia	19

BINET CLASSIFICATION³

Stage	Characteristics	Median Survival (months)
A	Three involved lymphoid sites	Comparable to age-matched controls
B	Three or more involved lymphoid sites	84
C	Anemia (Hgb <10 g/dL) and/or thrombocytopenia (platelets <100,000/ μ L)	24

Five sites of involvement: cervical, axillary and inguinal lymph nodes, spleen, and liver

- Rai and Binet classifications do not distinguish stable from more aggressive, rapidly evolving disease

Pearls of the History and Physical Examination¹

- 70%-80% of patients are asymptomatic at diagnosis and are discovered through routine blood screening
- Initial history should focus on:
 - Family history of lymphoid malignancy
 - Susceptibility to infection
 - Fever, night sweats, weight loss, fatigue, symptoms of anemia and thrombocytopenia
- Initial physical findings
 - Peripheral lymphadenopathy
 - Hepatosplenomegaly
 - Bulky intra-abdominal lymphadenopathy

Diagnostic Studies and Laboratory Values

- Minimum diagnostic requirements⁴
 - Peripheral blood
 - Absolute lymphocyte count (ALC) >10,000/ μ L, with a preponderance of mature-appearing cells⁴
- $$\text{ALC} = (\text{WBC (cells}/\mu\text{L}) \times \% \text{ lymphocytes})/100$$

- ALC between 5000 and 10,000/ μ L requires lymphocytic phenotyping by flow cytometry: predominance of single B-cell marker identifies monoclonal lineage—low levels of SmIg and either κ or λ light chains (not both); B-cell-associated antigen expression (CD19, CD20, CD21, CD23, CD24); T-cell antigen expression (CD5)
- Bone marrow: normocellular to hypercellular with lymphocytes $>30\%$ of all nucleated cells
- Evaluations at diagnosis to identify high-risk patients: staging, lymphocyte doubling time, β_2 -microglobulin, cytogenetics/FISH analysis, CD38 status, and IgV_H gene mutation status⁵
- Additional investigations at diagnosis or through the course of the disease¹
 - Direct antiglobulin test (Coombs' test)
 - Reticulocyte count
 - Renal and liver biochemistry (including urate levels)
 - Quantitative serum immunoglobulins (IgG, IgM, IgA)
 - Chest x-ray
 - Lymph node biopsy
 - Abdominal computed tomography scan

Guide to Acute Management

- Decide whether to treat at diagnosis or during disease progression
- Indications for treatment⁶
 - Constitutional symptoms: weight loss $>10\%$ body weight in <6 months, fever in absence of infection, night sweats, extreme fatigue
 - Marrow failure: progressive anemia or thrombocytopenia
 - Massive splenomegaly (>6 cm below costal margin)
 - Massive lymphadenopathy (>10 cm in largest dimension)

- More than 50% increase in ALC in <2 months
- Autoimmune hemolytic anemia or immune thrombocytopenic purpura refractory to other therapies
- Recurrent infections

Treatment

- No clear curative modality exists; only potentially curative therapy is allogeneic transplantation⁷
 - Disease-free survival 25%-60%
 - Treatment-related mortality rate 30%-40%
 - Consider in patients <65 years old or with fludarabine-resistant disease
- Chemotherapy: alkylating agents (chlorambucil) with or without corticosteroids, or purine analogs (fludarabine)
- Radiation therapy: for bulky lymphadenopathy
- Splenectomy
- Immunotherapy
- Monoclonal antibodies

Complications

- Infection: due to functional immunological deficiency
 - Major contributing factors: disease progression, therapy-induced immune dysfunction, and neutropenia⁸
 - Monthly intravenous immunoglobulins may benefit patients with documented recurrent bacterial infections and low serum immunoglobulins
- Immune dysregulation⁹
 - Autoimmune hemolytic anemia (11% of advanced-stage patients)
 - Idiopathic thrombocytopenia (2%-3% of patients)
 - Pure red cell aplasia (6% of patients)
 - Most respond to prednisone
- Malignant transformation into another lymphoproliferative disorder: usually a terminal event
 - Prolymphocytic leukemia (10%)¹⁰

- Diffuse large B-cell lymphoma (Richter's transformation) (3%)¹¹
- Hodgkin's disease (0.5%)¹²
- Multiple myeloma (0.1%)
- Second malignancies: usually lung, brain, skin or gastrointestinal tract¹³



Patient Care Warnings

- In later stages of disease, after multiple courses of treatment, patients can become immunologically devastated; therefore, infections can be severe and life-threatening

References

- ③ 1. Oscier D, Fegan C, Hillmen P, et al. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. *Br J Haematol* 2004;125:294.
- ③ 2. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;46:219-34.
- ② 3. Binet JL, Lepoprier M, Dighiero G, et al. A clinical staging system for chronic lymphocytic leukemia: Prognostic significance. *Cancer* 1977;40:855-64.
- ③ 4. International Workshop on Chronic Lymphocytic Leukemia. Chronic lymphocytic leukemia: Recommendations for diagnosis, staging and response criteria. *Ann Intern Med* 1989; 110:236.
- ③ 5. Shanafelt TD, Geyer SM, Kay NE. Prognosis at diagnosis: Integrating molecular biologic insights into clinical practice for patients with CLL. *Blood* 2004;103:1202.
- ③ 6. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-Sponsored Working Group guidelines for chronic lymphocytic leukemia: Revised guidelines for diagnosis and treatment. *Blood* 1996;87:4990-97.
- ③ 7. Jabbour E, Keating MJ, Champlin RE, et al. Stem cell transplantation for chronic lymphocytic leukemia: Should not more patients get a transplant? *Bone Marrow Transplant* 2004;34:289.
- ③ 8. Tsiodras S, Samonis G, Keating MJ, et al. Infection and immunity in chronic lymphocytic leukemia. *Mayo Clin Proc* 2000;75:1039.

- ③ 9. Diehl LF, Ketchum LH. Autoimmune disease and chronic lymphocytic leukemia: Autoimmune hemolytic anemia, pure red cell aplasia, and autoimmune thrombocytopenia. *Semin Oncol* 1998;25:80.
- ② 10. Melo JV, Catovsky D, Galton DAG. The relationship between chronic lymphocytic leukaemia and prolymphocytic leukaemia: Patterns of evolution of "prolymphocytoid" transformation. *Br J Haematol* 1986;64:77.
- ② 11. Robertson LE, Pugh W, O'Brien S, et al. Richter's syndrome: A report on 39 patients. *J Clin Oncol* 1993;11:1985.
- ② 12. Ohno T, Smir BN, Weisenburger DD, et al. Origin of the Hodgkin/Reed-Sternberg cells in chronic lymphocytic leukemia with "Hodgkin's transformation." *Blood* 1998; 91:1757.
- ② 13. Travis LB, Curtis RE, Hankey BF, et al. Second cancers in patients with chronic lymphocytic leukemia. *J Natl Cancer Inst* 1992;84:1422.

CHRONIC MYELOGENOUS LEUKEMIA (CML)

Definition, Etiology, and Epidemiology

- Malignant disorder of hematopoietic stem cells that results in clonal proliferation of mature myeloid cell and myeloid hyperplasia in bone marrow (BM) and increases in erythroid cells and platelets in peripheral blood¹
- Develops when a single, pluripotential, hematopoietic stem cell acquires chromosomal translocation, resulting in creation of breakpoint cluster region (BCR)–Ableson leukemia virus (ABL) fusion protein
- Fusion of BCR gene on chromosome 22 to ABL gene on chromosome 9 creates a constitutively active cytoplasmic tyrosine kinase^{2,3}
 - Philadelphia chromosome t(9;22) detected in 95% of patients
 - Complex or variant translocation detected in 5% of patients
- Incidence of 1-2 cases per 100,000 people per year
- Accounts for 15% of adult leukemia

- Median age at diagnosis 45-55 years
- Slight male predominance⁴

Pearls of the History and Physical Examination

- 40% of patients are asymptomatic at diagnosis and are discovered only through routine serological studies¹

Symptoms⁵

- Fatigue, bleeding, anorexia, weight loss, night sweats, abdominal fullness

Physical Examination Findings

- Splenomegaly, purpura, hepatomegaly

Diagnostic Studies and Laboratory Values¹

Peripheral Blood Findings

- Elevated white blood cell (WBC) count (usually $>25,000/\text{mm}^3$)
 - All stages of neutrophil maturation (promyelocyte → myelocyte → metamyelocyte → band → neutrophil) visible on peripheral smear
 - Classically, more myelocytes than metamyelocytes (“leukemic hiatus”)⁶
- Elevated platelet count (30%-50% of patients)
- Basophilia and eosinophilia ($>90\%$ of patients)
- Low leukocyte alkaline phosphatase activity (as opposed to high levels in infection) (rarely done)
- Patients with a complex or variant translocation tend to have monocytosis and a low neutrophil/monocyte ratio in peripheral smear⁷

Bone Marrow

- Hypercellularity, reduced fat content
- Increased ratio of myeloid to erythroid cells

- Increased numbers of megakaryocytes
- Blasts and promyelocytes constitute less than 10% of all cells

Gold Standard

- Diagnosis must be confirmed with detection of Philadelphia chromosome or its fusion protein (via cytogenetics, fluorescence in situ hybridization, or polymerase chain reaction)

Triphasic Clinical Course⁴

Chronic Phase

- Characterized by large increases in committed myeloid progenitor cells in marrow, resulting in leukocytosis and thrombocytosis
- Present in 85% of adults at time of diagnosis
- Blasts usually <2% of peripheral WBCs, <10% of BM nucleated cells

Accelerated Phase

- Progressively impaired neutrophil differentiation; leukocyte counts increasingly difficult to control; one or more of the following present:
 - Blasts 10%-19% of WBCs in peripheral blood and/or nucleated cells in BM
 - Peripheral blood basophil $\geq 20\%$
 - Persistent thrombocytopenia (<100 k) unrelated to therapy or persistent thrombocytosis (>1 million) unresponsive to therapy
 - Increasing spleen size and increasing WBC numbers unresponsive to therapy
 - Cytogenetic evidence of clonal evolution

Blast Phase

- Aggressive and rapidly fatal disease resembling acute leukemia; progression usually occurs 3-5

years after diagnosis, 3-18 months after onset of accelerated phase; can be either myeloid or lymphoid; one or more of the following present:

- Blasts $\geq 20\%$ of peripheral blood WBCs or nucleated cells in BM
- Extramedullary blast proliferation
- Large foci or clusters of blasts in BM biopsy

Prognosis

- Prior to imatinib mesylate (Gleevec) therapy, death was expected in 10% of patients in first 2 years and 20% yearly thereafter, with a median survival of 4 years; long-term outcomes with the use of Gleevec undetermined

Guide to Acute Management

Hematopoietic Stem Cell Transplantation

- Results directly related to phase of disease at time of diagnosis; highest survival rate (70%) seen in patients transplanted within 1 year of diagnosis in chronic phase⁸
- Preferred treatment for younger patients (<60 years old) with newly diagnosed CML in the chronic phase

Gleevec

- Selective inhibitor of aberrant tyrosine kinase, which results from Philadelphia chromosome
- Improved response rates compared with interferon + cytarabine⁹
 - Hematological response (97% vs. 69%)
 - Cytogenetic response (76% vs. 14%)
- Durability of response not yet determined
- Use considered most appropriate in older patients (not eligible for transplantation) or younger patients without a suitable donor as well as for patients in accelerated or blast phase¹⁰

Oral Chemotherapy¹¹

- Hydroxyurea preferred over busulfan (median survival 58 months vs. 45 months)
- Up to 90% hematological response
- Rarely achieves cytogenetic response (<35% Philadelphia chromosome-positive cells)
- Does not prolong overall survival
- Must be considered only palliative therapy

Interferon- α ¹²

- 80% of patients achieve hematological response
- 30% of patients achieve complete cytogenetic response
- Significant toxicity in majority of treated patients: fever, chills and flu-like symptoms
- Combined treatment with cytarabine (Ara-C) may provide survival benefit; however, results have been mixed^{13,14}

**Patient Care Warnings**

- Hyperleukocytosis better tolerated than in acute leukemia
- Symptoms of leukostasis (headache, blurred vision, retinal hemorrhage, pulmonary infiltrates) seen in accelerated and blast phase with WBC counts over 200,000/mm³¹⁵
- Hydroxyurea has favorable effect on blood viscosity levels

References

- ③ 1. Sawyers CL. Chronic myeloid leukemia. *N Engl J Med* 1999; 340:1330-40.

- ③ 2. Kurzrock R, Gutterman JU, Talpaz M. The molecular genetics of Philadelphia chromosome-positive leukemias. *N Engl J Med* 1988;319:990-98.
- ② 3. Specchia G, Mininni D, Guerrasio A, et al. Ph-positive acute lymphoblastic leukemia in adults: Molecular and clinical studies. *Leuk Lymphoma* 1995;18(Suppl 1):37-42.
- ③ 4. Faderl S, Talpaz M, Estrov Z, et al. The biology of chronic myeloid leukemia. *N Engl J Med* 1999;341:164.
- ② 5. Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. *Br J Haematol* 1997;96:111.
- ② 6. Spiers AS, Bain BJ, Turner JE. The peripheral blood in chronic granulocytic leukaemia: Study of 50 untreated Philadelphia-positive cases. *Scand J Haematol* 1977;18:25.
- ② 7. Ravandi F, Cortes J, Albitar M, et al. Chronic myelogenous leukaemia with p185BCR/ABL expression: Characteristics and clinical significance. *Br J Haematol* 1999;107:581.
- ② 8. Biggs JC, Szer J, Crilley P, et al. Treatment of chronic myeloid leukemia with allogeneic bone marrow transplantation after preparation with BuCy2. *Blood* 1992;80:1352.
- ① 9. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348:994.
- ③ 10. Johnson JR, Bross P, Cohen M, et al. Approval summary: Imatinib mesylate capsules for treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase. *Clin Cancer Res* 2003;9:1972.
- ① 11. Helmann R, Heimpel H, Hasford J, et al. Randomized comparison of busulfan and hydroxyurea in chronic myelogenous leukemia: Prolongation of survival by hydroxyurea. *Blood* 1993;82:398-407.
- ② 12. Kantarjian HM, Smith TL, O'Brien S, et al. Prolonged survival in chronic myelogenous leukemia after cytogenetic response to interferon-alpha therapy. The Leukemia Service. *Ann Intern Med* 1995;122:254.
- ① 13. Guilhot F, Chastang C, Michallet M, et al. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. *N Engl J Med* 1997;337:223.
- ① 14. Baccarani M, Rosti G, de Vivo A, et al. A randomized study of interferon-alpha versus interferon-alpha and low-dose arabinosyl cytosine in chronic myeloid leukemia. *Blood* 2002;99:1527.
- ② 15. Sharma K, Rao S, Bhat SV. Effect of hydroxyurea on blood viscosity in chronic myelogenous leukemia with hyperleukocytosis. *Physiol Chem Phys Med NMR* 1991;23:261-68.

HODGKIN'S DISEASE

Definition, Etiology, and Epidemiology

- Malignant neoplasm of lymphoid tissue characterized by the presence of Hodgkin/Reed-Sternberg cells in a background of inflammatory cells
- Based on histopathological features, there are two main classes of disease:
 - Classic Hodgkin's disease (HD)
 - Nodular sclerosis
 - Mixed cellularity
 - Lymphocyte-rich
 - Lymphocyte-depleted
 - Lymphocyte-predominant Hodgkin's disease (LPDH)
- Reed-Sternberg cells: origins unknown in most types of HD; in LPDH they are monoclonal B-cell neoplasms that have undergone extensive clonal immunoglobulin gene rearrangements
- Activate transcription factors such as nuclear factor-kappa beta, resulting in secretion of various cytokines and chemokines that recruit inflammatory cells
- Epstein-Barr virus (EBV) infection has been implicated as an initiating factor in cause of HD¹
- 7500 new cases of HD and 1500 deaths from HD in United States each year
- Bimodal age distribution: peaks in third decade and after age 50 years
- Predominant subtypes
 - Nodular sclerosis in young adults
 - Mixed cellularity in older population
- Higher socioeconomic status correlated with higher incidence of nodular sclerosis HD in young adults in developed countries²
- Lower socioeconomic status usually associated with

mixed cellularity subtype in children or elderly patients in developing countries²

- Infectious agents (e.g., Ebola virus), genetic factors, and immunocompromised states have been associated with increased risk for HD

Pearls of the History and Physical Examination

History

- Patients usually present with painless cervical or supraclavicular lymphadenopathy; however, can be painful after drinking beer
- Chest pain, cough, or superior vena cava syndrome associated with bulky mediastinal disease
- Inquire about “B” symptoms as this portends a worse prognosis: night sweats, fevers, weight loss >10% of baseline in 6 months
- Pel-Ebstein fever: high fever alternating with afebrile state; suggestive of HD
- Other symptoms: generalized pruritis, recurrent infections

Physical Examination

- Requires a thorough examination of all lymph node regions

Diagnostic Studies and Laboratory Values

Diagnostic Studies

- Excisional lymph node biopsy for histology and immunohistochemical studies to confirm diagnosis and determine subtype
- Computed tomography (CT) scan of chest, abdomen, and pelvis for staging
- In patients with mediastinal lymphadenopathy, calculate mediastinal mass ratio (MMR)³
 - Ratio of the maximal transverse diameter of the

mass to the maximal transverse intrathoracic diameter

- MMR >0.35 on CT or >0.33 on chest x-ray defines bulky disease and indicates a poorer prognosis
- Positron emission tomography and gallium scans are adjunctive imaging studies in patients with equivocal CT scan results
- Bilateral bone marrow biopsy

Laboratory Values

- Complete blood count with differential: anemia, mild leukocytosis, lymphopenia common
- Low serum albumin and elevated alkaline phosphatase
- Elevated lactate dehydrogenase and erythrocyte sedimentation rate
- Elevated serum β_2 -microglobulin
- Elevated serum levels of cytokines such as IL-6 and IL-10, soluble CD30, and soluble CD25 (although not clinically useful)

Ann Arbor Staging System⁴

- Stage I: involvement of single lymph node region (I) or a single extralymphatic organ or site (IE)
- Stage II: involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
- Stage III: involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
- Stage IV: diffuse or disseminated involvement of one or more extralymphatic organs or sites with or without associated lymph node involvement
- The absence or presence of “B” symptoms is noted by the suffix letters A or B, respectively

Guide to Acute Management

Classic HD⁵

- Stage I/II with favorable or low risk: no “B” symptoms or bulky disease and ≤ 1 extranodal site
 - Three to four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by involved-field radiotherapy or subtotal lymphoid irradiation
 - In young women, radiotherapy may be omitted to avoid secondary breast cancers; treat with six cycles of chemotherapy as an alternative
- Stage I/II with high risk: “B” symptoms or bulky disease present
 - Four to six cycles of ABVD, followed by involved-field radiotherapy
- Stage III/IV
 - Six to eight cycles of ABVD (two cycles after achieving complete response)

Lymphocyte Predominant Hodgkin's Disease (LPHD)

- Unlike HD, LPHD does not spread contiguously; it is indolent in nature and has a more favorable prognosis
- Most patients present with stage I disease
- Treat with involved-field radiotherapy alone
- Chemotherapy (ABVD) only for the few patients with stage III or IV disease
- Rituximab (chimeric anti-CD20 monoclonal antibody) can be used

Recurrent HD

- Autologous hematopoietic cell transplantation is the treatment of choice for patients younger than 70 years who fail induction or who relapse after chemotherapy or combined modality therapy⁶
- Salvage chemotherapy can be initiated prior to

transplantation or in patients with favorable features at relapse⁷

- Usually etoposide, methylprednisolone, high-dose ara-C, and cisplatin (ESHAP) or ifosphamide, cisplatin, and etoposide (ICE)

Prognosis

- Less favorable prognosis associated with:⁸
 - Male gender
 - Age ≥ 45 years
 - Stage IV disease
 - Presence of “B” symptoms
 - Anemia (hemoglobin < 10.5 g/dL)
 - Leukocytosis $\geq 15,000$ cells/mm³
 - Lymphopenia < 600 or $< 8\%$ of white blood cells
 - Serum albumin < 4 g/dL



Patient Care Warnings

- Long-term complications from HD treatment: secondary malignancies due to alkylating agents (acute myeloid leukemia, myelodysplasia), solid tumors due to radiotherapy (breast, lung, soft-tissue sarcomas, etc.), radiation pneumonitis, cardiac diseases (pericarditis, myocardial infarction, congestive heart failure), thyroid function abnormalities, and infertility

References

- ② 1. Johansson B, Klein G, Henle W, et al. Epstein-Barr virus (EBV)-associated antibody patterns in malignant lymphoma and leukemia: Hodgkin's disease. *Int J Cancer* 1970;6:450-62.
- ③ 2. Gutensohn N, Cole P. Epidemiology of Hodgkin's disease. *Semin Oncol* 1980;7:92-132.
- ② 3. Mauch P, Goodman R, Hellman S. The significance of medi-

- astinal involvement in early stage Hodgkin's disease. *Cancer* 1978;42:1037.
- ③ 4. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. *Cancer Res* 1971;31:1860.
 - ③ 5. Bonfante V, Santoro A, Viviani S, et al. ABVD in the treatment of Hodgkin's disease. *Semin Oncol* 1992;19(Suppl 5):38.
 - ③ 6. Mink SA, Armitage JO. High-dose therapy in lymphomas: A review of the current status of allogeneic and autologous stem cell transplantation in Hodgkin's disease and non-Hodgkin's lymphoma. *Oncologist* 2001;6:247-56.
 - ① 7. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992;327:1478.
 - ② 8. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. *N Engl J Med* 1998;339:1506.

NON-HODGKIN'S LYMPHOMA

Definition, Epidemiology, and Etiology

- Non-Hodgkin's lymphoma (NHL) is heterogeneous group of malignancies of B cells or T cells, distinct from Hodgkin's disease (HD), that are defined by their morphology, immunophenotype, genetic, and clinical features^{1,2}
- Make up 4% of new cancer diagnoses, with approximately 4% of cancer deaths, males > females, most common in white males^{3,4}

Etiology⁵

- Environmental factors: radiation, chemicals, herbicide
- Infectious agents: human T-cell lymphotropic virus-I, Ebola virus (EBV), *H. pylori*, human herpesvirus-8 (HHV-8), hepatitis C
- Immunosuppression: solid organ transplant, HIV/AIDS
- Other: post-HD treatment, chromosomal translocations

Diagnosis and Staging⁶

History

- Painless adenopathy (may wax and wane)
- “B” symptoms (fever, night sweats, loss of 10% of body weight within 6 months)
- Risk factors as noted above
- Gastrointestinal symptoms and Waldeyer’s ring (most common extranodal site)
- Neurological symptoms (especially with HIV patients)
- Skin findings (common with T-cell lymphomas)
- Testicular changes

Physical Examination

- Complete lymph node examination
- Waldeyer’s ring (base of tongue, tonsils)
- Examine liver, spleen, skin

Laboratory Studies

- Complete blood count with differential, serum chemistries, uric acid, alkaline phosphatase
- Prognostic: lactate dehydrogenase, albumin, β_2 -microglobulin

Other Studies

- Computed tomography chest/abdomen/pelvis, lymph node biopsy (preferably excisional), and bone marrow biopsy with cytogenetics and immunophenotypic analysis; molecular analyses for gene rearrangements (T-cell receptor, translocations) useful if available; cerebrospinal fluid (CSF) cytology in HIV, stage IV, high International Prognostic Index (IPI), or paraspinal lesions

Ann Arbor Staging⁷

- I: Single lymph node (LN) region (I), single extranodal organ or site (IE)
- II: Two or more LN regions on the same side of the diaphragm (II) or localized involvement of extranodal organ or site (IIE)
- III: LN regions on both sides of the diaphragm (III), localized involvement of an extralymphatic organ or site (IIIE), spleen (IIIS), or both (IIISE)
- IV: Diffuse or disseminated involvement or one or more extranodal sites with or without LN involvement

Classification

- Revised European-American Lymphoma (REAL)/World Health Organization (WHO) based on Indolent (**I**), Aggressive (**A**), or Highly Aggressive (**HA**)^{1,8}
- B-cell neoplasm
 - Precursor B-cell neoplasm: precursor B-lymphoblastic leukemia/lymphoma (**HA**)
 - Mature B-cell neoplasms
 - Chronic lymphocytic leukemia (**I**)
 - B-cell prolymphocytic leukemia (**A**)
 - Lymphoplasmacytic lymphoma (**I**)
 - Splenic marginal zone lymphoma (**I**)
 - Hairy cell leukemia (**I**)
 - Plasma cell myeloma (**A**)
 - Solitary plasmacytoma of bone (**I**)
 - Extrasosseous plasmacytoma (**A**)
 - Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma) (**I**)

- Nodal marginal zone B-cell lymphoma (**I**)
- Follicular lymphoma (**I** for grades I and II, **A** for grade III)
- Mantle cell lymphoma (**A**)
- Diffuse large B-cell lymphoma (**A**)
- Mediastinal (thymic) large B-cell lymphoma (**A**)
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt's lymphoma/leukemia (**HA**)
- T-cell and putative natural killer (NK) cell neoplasm
 - Precursor T-cell neoplasm:
 - Precursor T-lymphoblastic lymphoma/leukemia (**HA**)
 - Blastic NK cell lymphoma
 - Peripheral T-cell and NK cell neoplasm
 - T-cell prolymphocytic lymphocytic leukemia (**A**)
 - T-cell large granular lymphocytic leukemia (**I**)
 - Aggressive NK cell leukemia
 - Adult T-cell leukemia/lymphoma
 - Extranodal NK/T-cell lymphoma, nasal type
 - Enteropathy-type T-cell lymphoma
 - Hepatosplenic T-cell lymphoma
 - Subcutaneous panniculitis-like T-cell lymphoma
 - Mycosis fungoides
 - Sezary syndrome (**I**)
 - Primary cutaneous anaplastic large-cell lymphoma
 - Peripheral T-cell lymphomas (PTCL), unspecified (**A**)
 - Angioimmunoblastic T-cell lymphoma (**A**)
 - Anaplastic large-cell lymphoma

Prognosis

- IPI for patients with aggressive NHL⁹
 - 1 point each for **A**ge >60, **P**erformance status ECOG 2–4, > **L**DH double the normal, >1 **E**xtranodal site of involvement, **S**tage III-IV disease (APLES)

Score	Risk Group	Complete Remission Rate	2-Year Survival	5-Year Survival
0-1	Low	87%	84%	73%
2	Low intermediate	67%	66%	51%
3	High intermediate	55%	54%	43%
4-5	High	44%	34%	26%

Guide to Acute Management

Indolent

- Untreated survival measured in years
- Stages I and II
 - “Watch and wait:” 5-year survival 97%, 10 years 85%, 20 years 22%, but symptomatic patients are usually treated¹⁰
 - XRT¹¹ or single agent chemotherapy (chlorambucil, fludarabine, rituximab¹²)
- Stages III and IV
 - “Watch and wait” versus treatment remains controversial¹³; treatment with various chemotherapy regimens (single agents, combinations such as CVP), XRT, immuno- and radioimmunotherapy, autologous stem cell transplant [ASCT]¹⁴)

Aggressive

- Untreated survival measured in months, treatment based on staging and IPI
- Initial treatment: CHOP + rituximab¹⁵; high-dose chemotherapy with ASCT in first remission for patients with high IPI score is controversial^{16,17}
- Relapse: multiple regimens including ICE, DHAP, ESHAP, EPOCH, MINE, MINT, MIME, and stem cell transplantation¹⁸
- T-cell lymphoma: treatment depends on type and location¹⁹

Highly Aggressive

- Untreated survival measured in weeks
- CODOX-M with IVAC for high-risk patients²⁰

RESPONSE CRITERIA²¹

Response Category	Physical Examination	Lymph Nodes	< Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CR [u]	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥ 50% decrease	Irrelevant
Relapse/Progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

CR= complete remission; CR [u] = complete response unconfirmed/uncertain; PR= partial response

EXTRANODAL NHL²²

Location	Pathology	Associations	Treatment
Stomach	B-cell MALToma	<i>H. pylori</i>	Antibiotics
Intestine	B-cell MALToma	Obstruction	Antibiotics
	PTCL	Celiac disease	Combination chemotherapy
	Small non-cleaved B-cell	Obstruction	High-dose cyclophosphamide

EXTRANODAL NHL²² (Continued)

Location	Pathology	Associations	Treatment
Waldeyer's ring	Large B cell		Combination therapy
Paranasal	Large B cell	Central nervous system (CNS) disease	CNS prophylaxis, combination therapy
Salivary gland	B-cell MALToma	Sjögren's syndrome	Chemotherapy, radiation therapy (XRT), or both
Thyroid	B cell	Hashimoto's thyroiditis	XRT or combination therapy
Lung	Small B cell, B-cell MALToma		Chemotherapy
Orbital	Small B cell, B-cell MALToma		Chemotherapy, XRT, or both
Primary CNS	Large B cell	AIDS, ocular involvement, leptomenigeal disease	Steroids, methotrexate, +/- XRT
Testis	Large B cell	Contralateral testis, CNS, retroperitoneal	Orchiectomy, combination chemotherapy, XRT to contralateral testis, CNS prophylaxis
Breast	Large B cell	Pregnancy	Combination chemotherapy +/- XRT
Ovary	Burkitt's lymphoma, large B cell	Bilateral disease	Combination chemotherapy
Bone	Large B cell		Combination chemotherapy +/- XRT
Cutaneous	<i>Mycosis fungoides</i> B-cell MALToma, first-degree cutaneous follicular or B-cell		Skin-directed Radiation if stage IE; B cell: combined therapy

HIV-Associated NHL²³

Epidemiology

- AIDS-defining disease in 3% of patients
- Increased risk for immunoblastic and diffuse large B-cell
- 35%-65% are EBV-positive
- HHV-8 is associated with primary effusion lymphoma (PEL)

Pathology

- Burkitt's lymphoma and Burkitt-like, B-cell immunoblastic, and PEL most common

Signs/Symptoms

- Enlarging mass, "B" symptoms, neurological symptoms (always evaluate CSF)

Prognosis

- Can use IPI²⁴

Treatment

- CHOP + highly active antiretroviral therapy,²⁵ dose-adjusted EPOCH²⁶
- Always give granulocyte colony stimulating factor support
- Need CSF prophylaxis with intrathecal chemotherapy

References

- ③ 1. Warkne RA, et al. A revised European-American classification of lymphoid neoplasm: A proposal from the International Lymphoma Study Group. *Blood* 1994;84:1361.
- ③ 2. Jaffe ES, et al. Hematopathology: Integration of morphologic features and biologic markers for diagnosis. *Mod Pathol* 1999;12:113.
- ③ 3. Jemal A, et al. Cancer statistics, 2004. *CA Cancer J Clin* 2004;54:8.

- ③ 4. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:2367.
- ③ 5. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:2366.
- ③ 6. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:2374.
- ③ 7. Carbone PP, Kaplan HS, Mushoff K, et al. Report of the committee: Non-Hodgkin's Disease Staging Classification. *Cancer Res* 1971;31:1860.
- ③ 8. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:2377.
- ② 9. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive Non-Hodgkin's lymphoma. *N Engl J Med* 1993;329:987.
- ② 10. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: Long-term follow-up of no initial therapy. *J Clin Oncol* 2004;22:1454.
- ② 11. MacManus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. *J Clin Oncol* 1996;14:1282.
- ② 12. Colombat P, Salles G, Brousee N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: Clinical and molecular evaluation. *Blood* 2001;97:101.
- ③ 13. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:2380-81.
- ③ 14. Hunault-Berger M, Ifrah N, Solal-Celigny P. Intensive therapies in follicular non-Hodgkin lymphomas. *Blood* 2002; 100:1141.
- ① 15. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. *N Engl J Med* 2002;356: 235.
- ① 16. Milpied N, Deconinck E, Gaillard F, et al. Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. *N Engl J Med* 2004;350:1287.
- ① 17. Gisselbrecht C, Lepage E, Molina T, et al. Shortened first-line high-dose chemotherapy for patients with poor-prognosis aggressive lymphoma. *J Clin Oncol* 2002;20:2472.
- ③ 18. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:2389.
- ③ 19. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:2383-86.

- ② 20. Magrath I, Adde M, Shad A, et al. Adults and children with small noncleaved-cell lymphoma have similar excellent outcome when treated with the same chemotherapy regimen. *J Clin Oncol* 1996;14:925.
- ③ 21. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. *J Clin Oncol* 1999;17:1244.
- ③ 22. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:2393.
- ③ 23. Greer JP, Foerster J, Lukens JN, et al. *Wintrobe's Clinical Hematology*, 11th ed. New York, Lippincott Williams & Wilkins, 2004:1883-85.
- ② 24. Rossi G, Donisi A, Casari S, et al. The International Prognostic Index can be used as a guide to treatment decisions regarding patients with human immunodeficiency virus-related non-Hodgkin lymphoma. *Cancer* 1999;86:2391.
- ① 25. Vaccher E, Spina M, di Gennaro G, et al. Concomitant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy plus highly active antiretroviral therapy in patients with human immunodeficiency virus-related non-Hodgkin lymphoma. *Cancer* 2001;91:155.
- ① 26. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: Pharmacodynamic approach with high efficacy. *Blood* 2002; 99:2685.

MULTIPLE MYELOMA AND OTHER PLASMA CELL DYSCRASIAS

Definition, Etiology, and Epidemiology^{1,2}

- Malignant clonal proliferation of plasma cells in the bone marrow, producing monoclonal protein (M protein) that may cause osteolytic lesions, anemia, hypercalcemia, and renal insufficiency
- The types of monoclonal proteins produced are IgG (60%), IgA (20%), IgD (2%), IgE (<0.1%), or light-chain κ or λ only (18%)
- Several factors have been potentially implicated in the etiology of multiple myeloma (MM)

- Environmental exposures: radiation/sheet metal workers/mineral oil
- Chronic inflammation
- Infection
- Human herpesvirus-8
- History of plasma cell proliferation disorders (e.g., monoclonal gammopathy of unknown significance)
- Approximately 4 cases per 100,000 annually
- Most common hematological malignancy in Western countries: 1% of all new cancer diagnoses, 10% of hematological malignancies, 2% of all cancer deaths
- Incidence in African Americans is twice that of whites
- More frequent in men than women
- Median age at presentation is 65 years
- 5-year and 10-year survival rate is 31% and 10%, respectively

Pearls of the History and Physical Examination

Symptoms^{1,2}

- May be asymptomatic
- Osteolytic lesions or pathological fractures: bone pain, radicular pain
- Anemia: fatigue, weakness
- Hypercalcemia: confusion, polyuria, nephrolithiasis, polydipsia, lethargy, nausea, vomiting, constipation.
- Renal insufficiency: nausea, vomiting, edema, dyspnea, symptoms of uremia, fluid overload; renal insufficiency is more common in patients with light-chain disease
- Infections: fever (classically encapsulated organisms such as *Streptococcus pneumoniae*, but other bacterial infections not uncommon)
- Extramedullary plasmacytoma may also present as a subcutaneous mass or local symptoms, depending on the site of the lesion

Physical Examination^{1,2}

- Patient may have unremarkable clinical examination
- Pallor
- Fever
- Organomegaly
- Bleeding (more common with IgA)
- Neurological syndromes secondary to cord/nerve root compression
- Rarely: extramedullary plasmacytomas may present as a mass in bone/soft tissue
- Signs of renal insufficiency: edema, volume overload
- Signs of amyloidosis: carpal tunnel syndrome, macroglossia, edema secondary to nephritic syndrome, signs of congestive heart failure secondary to cardiomyopathy
- Organomegaly: unusual

Diagnostic Studies and Laboratory Values^{1,2}

Blood Tests

- Complete blood count with differential: normocytic, normochromic anemia; leukopenia is less common; thrombocytopenia occurs only in very advanced cases
- Peripheral blood smear: Rouleaux formation, plasma cells
- Serum creatinine: increased in patients with renal failure (50%)
- Serum calcium: increased in about 30%-40% of patients
- Serum albumin and total protein (increased globulins/decreased albumin)
- Serum and urine protein electrophoresis (SPEP, UPEP) with immunofixation: reveals monoclonal paraproteins

- 24-hour urine collection for protein quantification: to identify light chains missed on the SPEP
- Quantitative immunoglobulins (uninvolved immunoglobulins may be decreased)
- Serum lactate dehydrogenase (LDH): may be elevated
- Serum β_2 -microglobulin: may be elevated

Bone Marrow Aspirate and Biopsy

- To determine the percentage of plasma cells

Plain Film Skeletal Survey

- To look for lytic lesions, pathological fractures, or generalized osteopenia; occasionally, patients can have osteosclerotic disease

Diagnostic Criteria for Myeloma

Major Criteria

- Plasmacytoma on tissue biopsy
- 30% plasma cells in the bone marrow
- Monoclonal protein levels >3.5 g/dL for IgG, >2 g/dL for IgA, or >1 g/dL urine light chains in 24 hours

Minor Criteria

- 10%-30% plasma cells in the bone marrow
- Presence of a monoclonal protein at lower concentrations than the first criterion above
- Lytic bone lesion(s)
- Abnormally low levels of immunoglobulins other than the monoclonal component
- Diagnosis of myeloma requires at least one major and one minor criteria or three minor criteria that include the first two criteria^{1,2}

Guide to Acute Management

Regimens

- Thalidomide/dexamethasone; vincristine, adriamycin/doxorubicin, and dexamethasone (VAD), and melphelan prednisone (MP)^{1,2}
 - MP: well tolerated and can be given orally, but responses can be slow to achieve; because of stem cell toxicity, should not be used in patients younger than 75 years who would be candidates for stem cell transplantation
 - VAD can result in faster response rates (thus, better for controlling symptoms), but requires a 4-day infusion and placement of a central venous catheter
 - VAD is less marrow-toxic than MP: can be used for induction chemotherapy before autologous transplantation
 - Thalidomide/dexamethasone³⁻⁵
 - Orally administered, rapid onset of action
 - Response rates better; comparable to those of VAD
 - Multiple side effects secondary to thalidomide (neuropathy, drowsiness, constipation); about 10% of patients on this regimen may have to discontinue treatment secondary to side effects
 - Do not use in women of childbearing age
 - Patients require anticoagulation because of high risk of deep vein thrombosis
- High-dose chemotherapy with autologous stem cell transplantation is the first-line therapy for patients with MM with stage II/stage III disease^{6,7}; autologous transplant carries low morbidity/mortality rate, improves survival, and is not thought to be curative

Allogeneic Transplantation

- Considered for young and relatively healthy patients who fail autologous transplantation and who have a

matched sibling donor; allogeneic transplantation can be curative but has high morbidity and mortality secondary to graft-versus-host disease

New Approaches

- Tandem autologous (two autotransplants) or tandem auto-miniallogeneic transplantations are new approaches to improving survival; now subject of national trials

Supportive Therapy

- Management of hypercalcemia: hydration, diuretics, bisphosphonates
- Intravenous (IV) bisphosphonates: e.g., pamidronate 90 mg given IV over 1-2 hours once a month; should be administered to all patients with skeletal involvement; monitor renal function and urine for albuminuria in patients on bisphosphonates
- Management of renal failure: may recover with treatment of MM in over 50% of cases; in severe cases, hemodialysis support may be needed
- Management of anemia: transfusions, erythropoietin to decrease need for transfusion
- Prevention and treatment of infection: most often due to encapsulated organisms as a result of deficient humoral immunity
 - All patients should get the pneumonia vaccine
 - Prophylaxis for *Pneumocystis carinii* pneumonia and fungal infection in patients on high-dose steroid regimens
- External beam radiation therapy to control refractory bone pain or to reduce mass effect in patients with spinal cord compression
- Prophylactic orthopedic stabilization for radiological fracture/impending fracture

Future Considerations

- Bortezomib in combination with dexamethasone for refractory or relapsed MM⁸

Prognosis in Multiple Myeloma

- Median survival with standard chemotherapy is 2-3 years^{1,2}
- Autologous stem cell transplantation improves 5-year survival rate from 12% with standard chemotherapy to 52%⁹
- Factors that correlate with poor prognosis: elevated β_2 -microglobulin ($>6 \mu\text{g/mL}$), elevated LDH, high plasma-cell labeling index, and chromosome 13 abnormalities^{1,2}

Other Plasma Cell Dyscrasias

Monoclonal Gammopathy of Unknown Significance (MGUS)

- Occurs in 1% of normal individuals >40 years old
- Approximately 25% of patients with MGUS develop MM macroglobulinemia or non-Hodgkin's lymphoma over 20 years (about 1% per year)
- M-component usually low risk of progression; higher in patients with relatively higher M-protein ($>1.5\text{gm/dL}$)
- 90% of patients with MGUS die from conditions other than progression of disease

Waldenström's Macroglobulinemia (WM)

- Characterized by lymphoplasmacytic bone marrow and tissue infiltrate, in addition to elevated IgM production²
- Usually affects people in the fifth to seventh decades of life

- Causes symptoms due to tumor infiltration (marrow, lymph nodes, spleen), circulating IgM (hyperviscosity, cryoglobulinemia, cold agglutinin hemolytic anemia), and tissue deposition of IgM (neuropathy, glomerular disease, amyloidosis)
- Treat hyperviscosity with plasmapheresis followed by chemotherapy
- Treatment of WM with alkylating agents and steroids, purine analogs¹⁰, anti-B-cell antibody (rituximab)

Amyloidosis

- 35% of MM patients have positive subcutaneous fat pad biopsy for amyloid; only 3% have clinical amyloidosis
- 20% of patients with primary amyloidosis have evidence of MM
- Results from organ deposition of amyloid fibrils consisting of the NH₂ terminal amino acid residues of the variable portion of the light-chain immunoglobulin molecule²
- Features include nephrotic syndrome, cardiomyopathy, hepatomegaly, neuropathy, carpal tunnel syndrome, macroglossia
- Diagnosis with apple-green birefringence on polarized light examination of subcutaneous fat stained with Congo red
- Survival is variable depending on manifestation; median survival in patients with major organ involvement about 12-18 months
- High-dose therapy with melphelan with autologous stem cell transplantation results in good complete response and improved survival
- Treat patients not eligible for transplant with PO melphalan and steroids; complete response is rare¹¹



Patient Care Warnings

- In patients with anemia and unexplained renal insufficiency, obtain UPEP even if the SPEP is negative for monoclonal proteins; this is because light chains are filtered in the urine and may be undetectable in the serum
- After the diagnosis of MM is confirmed, VAD is used as an initial chemotherapy if transplantation is considered; for those who do not qualify for transplantation, melphalan is used with or without corticosteroids

References

- ③ 1. Bataille R, Harousseau J. Medical progress: Multiple myeloma. *N Engl J Med* 1997;336:1657-64.
- ③ 2. Singer CRJ. ABC of clinical hematology: Multiple myeloma and related conditions. *Br Med J* 1997;314:960-63.
- ② 3. Barlogie B, Desikan R, Eddlemon P, et al. Extended survival in advanced and refractory myeloma after single-agent thalidomide: Identification of prognostic factors in a phase II study of 169 patients. *Blood* 2001;98:492-94.
- ② 4. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 2002;21:4319-23.
- ② 5. Weber D, Rankin K, Gavino M, et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol* 2003;21:16-19.
- ① 6. Attal M, Harousseau JL, et al. A prospective, randomized trial of autologous bone marrow transplant and chemotherapy in multiple myeloma. *N Engl J Med* 1996;335:91-97.
- ① 7. Femand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: Up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood* 1998;92:3131-36.
- ② 8. Kropff MH, Bisping G, Wenning D, et al. Bortezomib in combination with dexamethasone for relapsed multiple myeloma. *Leuk Res* 2005;29:587-90.
- ① 9. Attal M, Harousseau JL, Facon T, et al. Single versus double

autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003;349:2495-2502.

- ③ 10. Dhodapkar MV, Jacobson JL, Gertz MA, et al. Prognostic factors and response to fludarabine therapy in Waldenstrom's macroglobulinemia: Results of US intergroup trial. *Blood* 2001;98:41-48.
- ③ 11. Sanchorawala V, Wright DG, Seldin DC, et al. An overview of the use of high-dose melphalan with autologous stem-cell transplantation for the treatment of AL amyloidosis. *Bone Marrow Transplant* 2001;28:637-42.

LUNG CANCER

Definition, Etiology, and Epidemiology

- Accounts for more deaths in the United States than any other type of cancer in both men and women
- Third most common cancer in the United States, behind breast and prostate cancer

Histological Subtypes¹

- Small cell lung carcinoma (SCLC): approximately 18% of cases
- Non-small cell lung carcinoma (NSCLC): approximately 73% of cases, including squamous cell carcinoma (29%), adenocarcinoma (32%), large cell carcinoma (9%)
- Other pulmonary malignancies: carcinoid, mucoepidermoid carcinoma, adenoid cystic carcinoma, sarcoma

Pearls of the History and Physical Examination

Common Risk Factors

- Tobacco: accounts for approximately 90% of lung cancers in the United States (85% due to smoking, 5% from second-hand exposure)

- Women who smoke 1-20 cigarettes/day have a 10-fold increased risk for lung cancer compared with nonsmokers, >20 cigarettes/day carries a 21-fold increased risk
- Risk falls to 1.6 times that of nonsmokers following >16 years of smoking cessation²
- Tuberculosis: may result in development of a scar carcinoma, most commonly adenocarcinoma
- Asbestos exposure: carries a six-fold increased risk³
- Radiation exposure: environmental radon exposure most common

Common Clinical Presentations

- Cough, hemoptysis, dyspnea, weight loss
- Bone pain seen with hypertrophic osteoarthropathy or bony metastases
- Hoarseness with paralysis of left recurrent laryngeal nerve
- Headaches, seizures, or focal neurological symptoms seen with central nervous system metastases
- Swelling of arm/face with superior vena cava syndrome
- Wheezing or stridor with partial airway obstruction
- Pancoast's tumor: Horner's syndrome (ptosis, miosis, anhidrosis) plus pain in C7-T1 dermatome; result of apical lung tumor invading T1-T2 vertebrae and stellate ganglion
- Paraneoplastic syndromes
 - Syndrome of inappropriate antidiuretic hormone
 - Cushing's syndrome: mediated by ectopic adrenocorticotrophic hormone secretion, most commonly with small cell carcinoma and pulmonary carcinoid
 - Eaton-Lambert syndrome
 - Hypercalcemia of malignancy: mediated by PTH-related peptide; most commonly seen with squamous cell carcinoma

- Dermatomyositis
- Hypertrophic osteoarthropathy: most commonly with adenocarcinoma
- 65%-70% of patients with small cell carcinoma will have evidence of disseminated disease at presentation

Notable Physical Examination Findings

- Digital clubbing
- Pleural effusion with diminished breath sounds and dullness to percussion
- Pulsus paradoxus, hypotension, jugular venous distention with malignant pericardial effusion and tamponade
- Thin skin, central obesity, ecchymoses, hirsutism, purple striae characteristic of Cushing's syndrome
- Muscle weakness increasing with sustained contraction in Eaton-Lambert syndrome

Diagnostic Studies and Laboratory Values

- Sputum cytology (low yield, but may be best for central lesions)
- Transthoracic needle aspiration (fine needle aspiration) of lung mass: preferred for peripheral lesions
- Bronchoscopy with transbronchial needle aspiration of lung mass: preferred for central lesions
- Mediastinoscopy for lymph node biopsy
- Cytology of pleural or pericardial effusions if indicated

Noninvasive Staging of NSCLC⁴

- Computed tomography (CT) of chest, including cuts of the adrenals

- Fluorodeoxyglucose positron emission tomography analysis for mediastinal lymph node metastases may be indicated and may eliminate the need for mediastinal exploration⁵
- Consider magnetic resonance imaging (MRI) for superior sulcus tumors to rule out brachial plexus and/or vertebral body involvement
- MRI of brain recommended if stage II or greater⁶

Noninvasive Staging of SCLC⁷

- CT of chest and abdomen
- CT or MRI of brain
- Nuclear bone scan

INTERNATIONAL STAGING SYSTEM FOR LUNG CANCER

Tx		Nx		Mx	
T1	<3 cm without invasion more proximal than lobar bronchus	N0	No node involvement	M0	No distant metastases
T2	>3 cm or one of following: • Invasion of pleura • Atelectasis of less than entire lung • >2 cm from the carina	N1	Ipsilateral hilar or peribronchial nodes	M1	Distant metastases including nodules in different lobe
T3	Any of the following: • Invasion of chest wall • Involvement of mediastinal pleural, diaphragm, or pericardium • <2 cm from the carina	N2	Ipsilateral mediastinal or subcarinal nodes		

INTERNATIONAL STAGING SYSTEM FOR LUNG CANCER (Continued)

Tx		Nx		Mx
T4	Any of the following: • Invasion of mediastinum, heart, great vessels, trachea, esophagus, carina, vertebral bodies • Pleural or pericardial effusion • Satellite tumors within same lobe	N3	Contralateral nodes or scalene nodes or supraclavicular nodes	

Stage Ia – T1N0M0, Ib – T2N0M0; stage IIa – T1N1M0, IIb – T2N1M0 or T3N0M0; stage IIIa – T3N1M0 or T1-3N2M0, IIIb – TxN3M0 or T4NxM0; stage IV – TxNxM1

Guide to Acute Management

Non–Small Cell Lung Carcinoma⁶

- Stage I or II: surgery is standard therapy; 5-year survival rate is 75% for stage I and 10-year survival rate 67%^{8,9}
 - If medically inoperable, radiation is an acceptable alternative
- Stage III
 - If operable, neoadjuvant chemotherapy $\pm$ radiation may be considered: does not clearly improve survival rate
 - If inoperable, concurrent chemotherapy and radiation is the most effective treatment; results in cure in 15%-20% of patients
- Stage IV: chemotherapy improves survival and quality of life
- Adjuvant chemotherapy improves survival for stage IB-III disease

Small Cell Lung Carcinoma⁷

- Cisplatin/carboplatin-based or combination chemotherapy $\pm$ radiation as standard therapy
- If complete remission is achieved, prophylactic cranial radiation should be considered⁸

Hypercalcemia of Malignancy

- IV fluids $\pm$ loop diuretics to increase urinary calcium excretion
- Calcitonin: because of tachyphylaxis, this is usually effective only for <48 hours
- Bisphosphonates: peak effect achieved in 2-4 days

Syndrome of Inappropriate Antidiuretic Hormone

- Water restriction, demeclocycline

Cushing's Syndrome

- If unresectable tumor, can treat with adrenal enzyme inhibitors such as ketoconazole, mitotane, aminoglutethimide, metyrapone¹⁰

Eaton-Lambert Syndrome

- Plasmapheresis, immunosuppressive therapy, and anticholinesterase medications have variable results
- Treatment with 3,4-diaminopyridine or IV immunoglobulin can lead to improvement in muscle strength^{11,12}
- Therapeutic plasma exchange is generally not helpful^{13,14}



Patient Care Warnings

- All patients should be encouraged to quit smoking
- If the patient is a smoker, he or she is at risk for other primary malignancies such as head & neck cancers, second pulmonary malignancies, etc. (1%-2% per year risk of second malignancy)

References

- ③ 1. Fauci A, et al. *Harrison's Principles of Internal Medicine*, 14th ed. New York, McGraw-Hill, 1998.
- ② 2. Garfinkel L, et al. Lung cancer and smoking trends in the United States over the past 25 years. *Cancer J Clin* 1991;41:137-45.
- ② 3. Selikoff IJ, et al. Mortality experience of insulation workers in the United States and Canada, 1943-1976. *Ann NY Acad Sci* 1979;330:91-116.
- ③ 4. Silvestri GA, Tanoue LT, Margolis ML, et al. The noninvasive staging of non-small cell lung cancer: The guidelines. *Chest* 2003;123:147S-156S.
- ③ 5. Vansteenkiste JF. PET scan in the staging of non-small cell lung cancer. *Lung Cancer* 2003;42:S27-S37.
- ③ 6. <http://www.nccn.org/> NCCN clinical practice guidelines in oncology 2005. National Comprehensive Cancer Network.
- ③ 7. Simon GR, Wagner H. Small cell lung cancer. *Chest* 2003;123:259S-271S.
- ③ 8. Martini N, Ginsberg RJ. Treatment of stage I and II disease. In *Comprehensive Textbook of Thoracic Oncology*, Aisner J, et al (eds), Williams and Wilkins, Baltimore, 1996:339.
- ② 9. Martini N, Bains MS, Burt ME, et al. Incidence and local recurrence and second primary tumors in resected stage I lung cancer. *J Thorac Cardiovasc Surg* 1995;109:120.
- ③ 10. Miller JW, Crapo L. The medical treatment of Cushing's syndrome. *Endocr Rev* 1993;14:443-58.
- ③ 11. Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database of Systematic Reviews*. CD003279, 2003.
- ③ 12. McEvoy KM. Diagnosis and treatment of Lambert-Eaton myasthenic syndrome *Neuro Clin* 1994;12:387-99.
- ③ 13. Richardson GE, Johnson BE. Paraneoplastic syndromes in thoracic malignancies. *Curr Opin Oncol* 1991;3:320-27.
- ③ 14. Devita VT Jr, et al. *Cancer: Principles and Practice of Oncology*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2005.

COLORECTAL CANCER

Definition, Etiology, and Epidemiology¹

- Third most common cancer: 135,000 cases of colon cancer each year
- Risk factors: age, diet rich in fat and cholesterol,

inflammatory bowel disease and genetic predisposition, colonic polyps, alcohol consumption

- Majority are adenocarcinomas that arise from pre-existing adenomatous polyps

Pearls of the History and Physical Examination¹

- Often diagnosed during screening; usually asymptomatic
- Can present with abdominal pain, change in bowel habits, hematochezia and melena, anemia, weight loss
- Symptoms of tumor related to location
 - Right-sided lesions: symptoms of anemia and melena
 - Left-sided lesions: symptoms of obstruction, tenesmus, constipation, hematochezia
- Evaluate any person with unexplained anemia for colon cancer
- 20% of patients have distant metastatic disease on presentation: lymphatic, hematogenous, contiguous, and peritoneal dissemination
 - Because the intestinal tract drains via the portal system, the first site of hematogenous dissemination is usually the liver, followed by lungs, bone, and brain
 - Tumors arising from the distal rectum may metastasize to the lungs because the inferior rectal veins drain into the inferior vena cava
- Streptococcus bovis bacteremia and clostridium sepsis can occur in 10%-25% of patients with colon cancer

Diagnostic Studies and Laboratory Values¹

- Screening tests
 - Most groups recommend annual fecal occult blood tests with flexible sigmoidoscopy every 5 years or

colonoscopy every 10 years for average-risk patients over age 50 years

- Obtain complete blood count, serum chemistries, liver function tests; carcinoembryonic antigen (CEA) test can be used to monitor response to therapy or evidence of recurrence
 - Liver enzymes may be normal even in the setting of small hepatic metastases
 - CEA may be elevated in pancreatic and hepatobiliary disease
- The entire large bowel must be examined for the presence of synchronous malignancies: 3%-5% of colon cancer patients may have another focus of neoplastic disease
- Staging is accomplished by physical examination, computed tomography scan of abdomen and pelvis, chest x-ray

Stage	Lesion	5-Year Survival
I	T1 invasion of mucosa or T2 muscularis mucosa, N0 (no LN mets), M0 (no distant mets)	95%
II	T3 subserosa or T4 visceral peritoneum, N0, M0	87%
III	Any T, N1 (1-3 LN) or N2 (4 or more LN), M0	55%
IV	Any T, any N0, M1 (distant mets)	5%

Guide to Acute Management

- Standard therapy is surgery with intent to cure in 75% of cases; surgery often required for diagnosis, staging or palliation of obstruction or bleeding¹
- Adjuvant chemotherapy recommended for high-risk stage II and stage III disease
 - 5FU/leucovorin + oxaliplatin²

- Palliative chemotherapy recommended for stage IV colon cancer (improves median survival from 6 months with no treatment to 22 months with treatment)
- Risk of recurrent colorectal cancer dependent on initial stage of disease
 - Recommended endoscopic surveillance with colonoscopy 1 year after surgery and every 3 years thereafter



Patient Care Warnings

- Evaluate any patient with unexplained anemia for iron deficiency and colorectal cancer
- Early diagnosis is imperative and greatly influences prognosis

References

1. Midgley R, Kerr D. Colorectal cancer. *Lancet* 1999;353:391-99.
2. Andre T, Boni C, Mounedji-Boudiaf L, et al. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343-51.

PROSTATE CANCER

Definition, Etiology, and Epidemiology^{1,2}

- Most common noncutaneous cancer among men: accounts for ~ 36% of male cancers and 13% of all cancer death
- ~ 80% of prostate cancer is found in men older than 65 years

- Men have a 1 in 6 chance of developing prostate cancer
- Twice as common in African Americans as in whites
- Risk factors include family history, African American race, and high-fat diet³; benign prostatic hypertrophy and vasectomy are not risk factors

Pearls of the History and Physical Examination^{1,2}

- Patients are usually asymptomatic
- Initial symptoms, when present, may include obstructive urinary symptoms, dysuria, hematuria, and back and/or hip pain
- Most important part of the physical examination is the digital rectal examination (DRE)
 - Palpation of hard, irregular nodules are concerning for malignancy
 - Only the posterior surfaces of the lateral lobes of the prostate are palpable during examination; as a result, deeper nodules or nodules located elsewhere may be missed
- Screening in the asymptomatic population remains controversial: there is no evidence that screening decreases mortality or morbidity rate
 - US Preventive Services Task Force does not recommend routine screening⁴
 - American Cancer Society recommends that patients should have a DRE at age 40 years and be offered prostate-specific antigen (PSA) screening at age 50⁵

Diagnostic Studies and Laboratory Values^{1,2}

- PSA has a sensitivity of 70%-80% but lacks specificity; normal level considered to be <4 ng/mL
- PSA of 4–10 ng/mL has a positive predictive value of 20%-35%,⁶ whereas a level >10 ng/mL has a positive predictive value of 50%^{6,7}

- Transrectal ultrasound should be performed on any patient with an elevated PSA and nodule(s) on DRE: this will help guide biopsy (gold standard for diagnosis)

Staging of Prostate Cancer

- Gleason score: determined by the two most predominant histological patterns in the area of tumor; each area is assigned a number 1–5 (with 1 being the most well-differentiated, and 5 being poorly differentiated); the score is these two numbers added together
 - 2-4 = low-grade
 - 5-7 = intermediate-grade
 - 8-10 = high-grade
- Tumor, Nodes, Metastasis Staging
 - T1: Tumor not palpable or visible by imaging
 - T1a: Tumor not palpable, <5% of resected tissue with cancer
 - T1b: Tumor not palpable, >5% of resected tissue with cancer
 - T1c: Tumor identified by needle biopsy after PSA elevation
 - T2: Tumor confined to prostate
 - T2a: Tumor palpable, involves one lobe (<50%)
 - T2b: Tumor palpable, involves one lobe (>50%)
 - T2c: Tumor involves two lobes
 - T3: Tumor extends through prostatic capsule
 - T3a: Extracapsular extension
 - T3b: Extracapsular extension with seminal vesicle involvement
 - T3c: Tumor invades seminal vesicles
 - T4: Tumor fixed or invades adjacent structures
 - N0: No regional lymph node metastasis
 - N1: Regional lymph node metastasis
 - M0: No distant metastasis
 - M1: Distant metastasis

- Staging Group
 - I: T1a, N0, M0, any Gleason score
 - II: T1a, N0, M0, Gleason score 2, 3, or 4; T1b/c, N0, M0; T2, N0, M0
 - III: T3, N0, M0
 - IV: T4, N0, M0; any T, N1, M0; any T, any N, M1

Guide to Acute Management

- Treatment should be based on probability of organ-confined disease and life expectancy of the patient
- The clinical stage, Gleason score, and pretreatment PSA have been used to estimate the probability of organ-confined disease and are helpful for planning treatment
- Patients with a life expectancy >10 years and whose disease is localized should consider surgery as the first-line treatment: surgery results in an increased rate of progression-free survival⁸
- Surgery includes radical retropubic prostatectomy or radical perineal prostatectomy; complications include impotence, urinary incontinency, or urethral stricture
- Radiation therapy or implanted radioactive seeds are used as alternative treatments in patients with T1 or T2 disease; complications include impotence, bladder irritation, or rectal irritation
- Hormonal treatment based on fact that prostate cancer growth depends on testicular androgens; androgen deprivation, therefore, leads to regression of tumor in about 85% of patients⁹
 - Clearly indicated for palliation of symptomatic metastatic disease^{1,2}
 - Orchiectomy: decreases circulating testosterone by removing the organ in which 95% of the testosterone is produced
 - Luteinizing hormone-releasing hormone analogs: decrease luteinizing hormone and testosterone, inhibits pituitary luteinizing hormone production

- Anti-androgens: inhibit binding of testosterone to the androgen receptor
- Most men will eventually develop hormone-resistant prostate cancer; at that time, chemotherapy should be considered
- Mitoxantrone has been shown to decrease pain and improve quality of life, although no increase in overall survival
- Docetaxel has shown improvement in survival when compared with mitoxantrone regimen¹⁰
- Combination of estramustine and taxanes (docetaxel or paclitaxel) has also shown some survival advantage, but estramustine increases thromboembolic risk¹¹
- Consider palliation of painful bone metastases with radiation therapy



Patient Care Warnings

- Hypercalcemia from prostate cancer is uncommon
- Bone metastases from prostate cancer are usually osteoblastic in appearance, and skeletal complications such as pain, spinal cord compression, and pathological fractures are common
- Consider spinal cord compression in any patient with prostate cancer and increasing back pain: treat this as a medical emergency

References

- ③ 1. Catalona WJ. Management of cancer of the prostate. *N Engl J Med* 1994;331:996-1004.
- ③ 2. Garnick MB, Fair WR. Prostate cancer: Emerging concepts. *Ann Intern Med* 1996;125:118-25,205-12.

- ② 3. Giovannucci E, Rimm EB, Colditz GA, et al. A prospective study of dietary fat and risk of prostate cancer. *J Natl Cancer Inst* 1993;85:1571-79.
- ③ 4. US Preventive Services Task Force. Screening for prostate cancer: Recommendation and rationale. *Ann Intern Med* 2002;137:915-16.
- ③ 5. Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: Update of early detection guidelines for prostate, colorectal, and endometrial cancers. *CA Cancer J Clin* 2001;51:38-75.
- ② 6. Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate-specific antigen in the early detection of prostate cancer: Results of a multicenter clinical trial of 6,630 men. *J Urol* 1994; 151:1283-90.
- ③ 7. Coley CM, Barry MJ, Fleming C, et al. Early detection of prostate cancer: Prior probability and effectiveness of tests. The American College of Physicians. *Ann Intern Med* 1997;126:394-406.
- ① 8. Paulson DF. Randomized series of treatment with surgery versus radiation for prostate adenocarcinoma. In Wittes RE, ed. Consensus Development Conference on the Management of Clinically Localized Prostate Cancer. NCI Monographs, No. 7, Washington, D.C.: Government Printing Office, 1988, 127-31 (NIH Publication No. 88-3005).
- ① 9. The Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer [abstract]. *N Engl J Med* 1984;311:1281-86.
- ① 10. Tannock IF, de Wit R, Berry WR, et al for the TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-12.
- ① 11. Petrylak DP, Tangen C, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513-20.

BREAST CANCER

Epidemiology¹

- Accounts for 1 in 3 of all cancers diagnosed in the United States
- Most frequently diagnosed cancer in U.S. women
 - 1 in 8 lifetime risk

- Second most common cause of death from cancer in U.S. women
- Male breast cancer incidence increasing but remains low (approximately 0.2% of all male cancers)

Risk Factors

- Sociodemographic: age, gender, socioeconomic status
- Hereditary
 - Family history: only present in 10% of women diagnosed with breast cancer
 - Genetic mutations: BRCA1 and BRCA2 (60%-80% lifetime risk), p53 (Li-Fraumeni syndrome, 90% lifetime risk), CHEK2 (activates BRCA1)
 - Breast density
- Breast disease: ductal hyperplasia, complex fibroadenoma, sclerosing adenosis, diffuse papillomatosis, atypical lobular hyperplasia, lobular carcinoma in situ, ductal carcinoma in situ
- Hormonal factors: higher concentrations of and prolonged exposure to estrogen increase the risk of breast cancer
 - Endogenous: younger menarche (<12 years old), late parity (≥30 years old), nulliparity, late menopause (≥55 years old), active pregnancy (risk reduction conferred 10 years after birth)²
 - Breastfeeding (>16 months cumulatively) is protective
 - Exogenous
 - Oral contraceptives: preponderance of evidence supports no conferred increased risk³
 - Hormone replacement therapy: modestly increased risk, especially with long-term therapy⁴
- Dietary factors: obesity⁵, fat intake, alcohol consumption⁶
- Ionizing radiation⁷
- Gail model: computer model that uses a combination of risk factors to derive age-specific estimates of breast cancer risk⁸

Screening

Mammography⁹

- Detects 90% of screening-detected cancers
- No clear reduction in risk with early screening of patients who have first-degree relative having breast cancer
- Recommendation: every 1-2 years for ages 40-49 years, annually for ages 50-70 years, and continued if >70 years for life expectancy of >8-10 years
 - Reduction in mortality rate clearly defined for ages 50-70 years

Clinical Breast Examination

- Identifies 5%-10% of breast cancers not detected by mammography
- Yearly starting at age 40 years

Breast Self-Examination

- No improvement in mortality rate; increases rate of breast biopsy for benign disease¹⁰

Differential Diagnosis of Breast Mass

Benign Breast Disease

- No increased risk of breast cancer: fibrocystic disease, ductal ectasia, solitary papillomas, noncomplex fibroadenoma, squamous metaplasia, stromal fibrosis, mastitis, simple cyst
- Increased risk of breast cancer: ductal hyperplasia, sclerosing adenosis, diffuse papillomatosis, complex fibroadenomas, atypical lobular hyperplasia

In Situ Carcinoma

- 15%-30% of malignant lesions
- No evidence of cellular invasion into surrounding stroma¹¹

- Ductal carcinoma in situ (DCIS): 80%
 - Five architectural subtypes: comedocarcinoma, solid, cribriform, papillary, and micropapillary; majority with mixed growth pattern
 - Rates of detection increasing with increased rates of mammographic screening
 - Represents nearly half of mammographically detected breast cancer
- Lobular carcinoma in situ (LCIS): 20%
 - Incidental finding in breast tissue removed for another reason
 - Never palpable; not detectable on mammography
 - Not a premalignant lesion; a marker of increased breast cancer risk
 - Two times increased risk, life-long absolute risk of 1% per year
 - Subsequent cancers can be multicentric and bilateral

Invasive Carcinoma

- 70%-85% of malignant lesions
- Cellular invasion into surrounding stroma with potential for metastases¹¹

Histology	Rate	Comments
<i>Invasive ductal carcinoma</i>	79%	Adenocarcinoma arising from terminal ducts
<i>Invasive lobular carcinoma</i>	10%	Improved prognosis over invasive ductal carcinoma ¹¹ Metastasize to unusual locations*
<i>Mucinous, papillary, tubular, and medullary and metaplastic carcinoma</i>	11%	All carry a more favorable prognosis

*Peritoneum, retroperitoneum, leptomeninges (carcinomatous meningitis), gastrointestinal tract, ovaries, and uterus

Paget's Disease

- Disorder of the nipple and areola virtually always associated with an underlying in situ or invasive carcinoma

Inflammatory Breast Cancer

- Distinct form of locally advanced breast cancer characterized by erythema, edema, and warmth of skin of breast
- Tumor in dermal lymphatics on biopsy is pathological correlate for inflammatory breast cancer
- Carries a poor prognosis due to highly angiogenic and invasive nature, leading to rapid progression and high metastatic potential

Pearls of the History and Physical Examination

History

- Characteristics of breast mass: location, duration, means of discovery, change in size over time, variation with menstrual cycle, associated tenderness or nipple discharge
- Evaluation of risk factors

Physical Examination

- Should serve to help differentiate benign versus malignant lesions
- Characteristics of malignancy: solitary lesion; firm, immobile, irregular borders; size (>2 cm); overlying skin changes (peau d'orange, erythema, warmth)

Diagnostic Studies and Laboratory Values

Mammography

- Concerning findings: irregular margins, spiculation, clustered irregular microcalcifications

BI-RADS CLASSIFICATION OF MAMMOGRAPHIC FINDINGS¹²

Assessment Category	Probability of Malignancy (%)
1: Negative	0
2: Benign	0
3: Probably benign	<2
4: Suspicious	2-75
5: Highly suggestive of malignancy	>75

Ultrasound

- Primarily used in younger women to differentiate between solid and cystic masses and to provide guidance for interventional procedures; not useful in distinguishing between solid masses (operator-dependent)

Contrast-Enhanced Magnetic Resonance Imaging

- Being evaluated; may be beneficial in patients with mammographically occult lesions and lobular cancers and for evaluating extent of disease; limited by expense and high false-positive rates¹³

Biopsy

- Fine-needle aspiration: sensitivity 98%, specificity 97% if palpable mass¹⁴
- False-negative rates high (up to 30%) in nonpalpable lesions
- Core needle biopsy
 - Used for nonpalpable abnormalities in conjunction with either stereotactic or ultrasound guidance
- Wire localization and excision: especially useful in excision of DCIS

Evaluation of a Breast Mass

- Women age <30-35 years
 - Mammography not usually helpful because of breast density

- If no concerning physical findings or family history of breast cancer, can consider monitoring mass 3-14 days through menstruation to see if it regresses
- Evaluate with ultrasound: negative predictive value is high if cystic
- If solid mass, refer for fine-needle aspiration, core biopsy, or excisional biopsy, depending on local expertise
- Women age 30-35 years and older
 - Evaluate initially with mammography
 - Misses 10%-20% of clinically palpable breast cancers: need to evaluate with biopsy even if negative¹⁵
 - Fine-needle aspiration biopsy
 - If nonbloody fluid obtained, no further evaluation required
 - If fluid bloody, send for pathology test: cancer in 7% of cases¹⁶

Staging and Additional Evaluation

- Physical examination with careful attention to skin, contralateral breast, and ipsilateral axillary/supraclavicular lymph nodes
- Bilateral mammography
- Laboratory studies: complete blood count and liver function tests
- Further workup indicated if more advanced disease (stage III, see below): chest x-ray, chest and abdominal computed tomography, radionuclide bone scan
- Pretreatment assessment of left ventricular ejection fraction with multigated acquisition scan for patients who will receive anthracycline chemotherapy is often performed; however, some studies suggest it has limited impact on clinical decision-making¹⁷
- Surgical excision with axillary lymph node dissection
- Pathological tumor evaluation with tumor receptor analysis (ER/PR and *Her-2-neu* amplification)

TUMOR, NODES, METASTASIS STAGING¹⁸

Stage	Characteristics	TNM	10-Year Survival (%)
0	Carcinoma in situ	Tis N0 M0	—
I	Tumor <2 cm, no lymph nodes	T1 N0 M0	90
IIA	Tumor <2 cm + mobile ipsilateral lymph nodes, or tumor 2-5 cm without lymph nodes	T0-1 N1 M0 T2 N0 M0	81
IIB	Tumor 2-5 cm with mobile lymph nodes, or tumor >5 cm without lymph nodes	T2 N1 M0 T3 N0 M0	70
IIIA	Metastases to fixed ipsilateral nodes, or tumor >5 cm with mobile lymph nodes	T0-3 N2 M0 T3 N1 M0	59
IIIB	Tumor with extension to chest wall or skin	T4 any N M0	36
IIIC	Metastasis to ipsilateral supra- or infraclavicular lymph nodes	any T N3 M0	36
IV	Distant metastasis	any T/N M1	18

Management**Ductal Carcinoma In Situ**

- Total mastectomy used to be customary treatment given incidence of multicentric disease and high recurrence rate, but recent studies have demonstrated wide (1 cm margin) local excision with radiation therapy (breast conservation) as the preferred alternative therapy¹⁹
- Axillary dissection is not necessary
- Addition of tamoxifen to surgical therapy in initial study decreases ipsilateral recurrence rate²⁰

Lobular Carcinoma In Situ

- No need for additional local therapy after biopsy
- Tamoxifen reduces risk of invasive breast cancer by 56% at 4 years²¹

Stage I-III A and Operable IIIC

- Surgical resection: outcomes comparable with modified radical mastectomy and breast-conserving therapy (lumpectomy and breast radiation therapy)^{22,23}
- Axillary staging
 - Traditionally axillary dissection
 - Initial studies to evaluate efficacy of sentinel lymph node biopsy show promise; procedure depends on surgeon expertise²⁴
 - Sentinel lymph node biopsy reduces morbidity rate of axillary dissection (lymphedema) and has replaced axillary dissection in most private and academic centers
- Adjuvant systemic therapy
 - Preoperative chemotherapy to shrink tumor size and make breast-conserving therapy feasible²⁵
 - Postoperative chemotherapy: absolute benefit determined by tumor (size, grade, number of positive lymph nodes) and patient characteristics (age, *Her-2* status)²⁶
 - Consider for: all women under age 50 years; postmenopausal women with estrogen receptor (ER)-negative tumors; women with positive axillary lymph nodes or tumors >2 cm
 - Slight advantage of anthracycline-based regimen over more traditional cytoxan, methotrexate, 5-FU²⁷
- Hormonal therapy²⁸
 - Premenopausal women with ER/progesterone receptor (PR)-positive tumors: tamoxifen (first line); ovariectomy or luteinizing hormone-releasing hormone antagonist (second line)

- Postmenopausal women with ER/PR-positive tumors: tamoxifen or aromatase inhibitor

Locally Advanced (Inoperable Stage IIIB, IIIC) and Inflammatory Breast Cancer

- Combined modality therapy with induction (neoadjuvant) chemotherapy²⁹
 - For patients who respond to induction chemotherapy: subsequent local therapy may include surgical resection, radiation therapy, or both
 - Hormonal therapy should be administered for ER-positive or unknown tumors

Stage IV (Metastatic) Disease

- Most common distant sites of metastases are bones, liver, and lung
- Therapy is palliative, with goals of therapy being improved quality and prolongation of life
- Surgery may be indicated for fungating/painful lesions, isolated metastases, or metastases with complications (pleural effusion, pathological fracture, etc.)
- Radiation therapy is important in palliation of localized symptomatic metastases
- Bisphosphonate therapy is routinely administered in patients with bony metastases for pain control and to reduce complications of metastases³⁰
- Hormonal therapy should be considered for initial therapy in postmenopausal ER/PR-positive or unknown disease
 - Superior response rates seen with anastrozole over tamoxifen³¹
 - Consider hormonal therapy for patients with ER-positive disease and bony metastases; chemotherapy is preferable for patients with extensive visceral metastases

- Trastuzumab (Herceptin) is a monoclonal antibody directed against the *Her-2-neu* receptor which may be used in combination with chemotherapy³¹
- Chemotherapy demonstrates an initial response rate of 50%-75%, and a variety of single agent or combination regimens exist



Patient Care Warnings

- Failure to diagnose breast cancer is one of the most frequent malpractice claims
- Patient preferences should be considered when developing a strategy for evaluation of breast masses
- Inflammatory breast cancer is a rapidly progressive disease with high rates of metastatic spread that must be treated with neoadjuvant chemotherapy $\pm$ radiation therapy prior to surgery

References

- ③ 1. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer J Clin* 2004;54:8-29.
- ② 2. Clemons M, Goss P. Estrogen and the risk of breast cancer. *N Engl J Med* 2001;344:276-85.
- ③ 3. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med* 2002; 346:2025-32.
- ① 4. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial. *J Am Med Assoc* 2003;289: 3243-53.
- ② 5. Lahmann PH, Lissner L, Gullberg B, et al. A prospective study of adiposity and postmenopausal breast cancer risk: The Malmo Diet and Cancer Study. *Int J Cancer* 2003;103: 246-52.

- ② 6. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: A pooled analysis of cohort studies. *J Am Med Assoc* 1998;279:535-40.
- ③ 7. John EM, Kelsey JL. Radiation and other environmental exposures and breast cancer. *Epidemiol Rev* 1993;15:157-62.
- ③ 8. Fletcher SW, Elmore JG. Mammographic screening for breast cancer. *N Engl J Med* 2003;348:1672-80.
- ② 9. Costantino JP, Gail MH, Pee D, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. *J Natl Cancer Inst* 1999;91:1541-48.
- ③ 10. Kusters JP, Gotzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. *Cochrane Database Syst Rev* 2003; CD003373.
- ③ 11. Kumar V: Robbins and Cotran: Pathologic Basis of Disease, 7th ed, Philadelphia, WB Saunders, 2005:1142-45.
- ② 12. Orel SG, Kay N, Reynolds C, et al. BI-RADS categorization as a predictor of malignancy. *Radiology* 1999;211:845-50.
- ② 13. Tillman GF, Orel SG, Schnall MD, et al. Effect of breast magnetic resonance imaging on the clinical management of women with early-stage breast carcinoma. *J Clin Oncol* 2002;20:3413-23.
- ② 14. Ljung BM, Drejet A, Chiampi N, et al. Diagnostic accuracy of fine-needle aspiration biopsy is determined by physician training in sampling technique. *Cancer* 2001;93:263-68.
- ② 15. Barlow WE, Lehman CD, Zheng Y, et al. Performance of diagnostic mammography for women with signs or symptoms of breast cancer. *J Natl Cancer Inst* 2002;94:1151-59.
- ② 16. Ciatto S, Cariaggi P, Bulgaresi P. The value of routine cytologic examination of breast cyst fluids. *Acta Cytol* 1987;31:301-304.
- ② 17. Sabel MS, Levine EG, Hurd T, et al. Is MUGA scan necessary in patients with low-risk breast cancer before doxorubicin-based adjuvant therapy? *Am J Clin Oncol* 2001;24:425-28.
- ③ 18. Woodward WA, Strom EA, Tucker SL, et al. Changes in the 2003 American Joint Committee on Cancer Staging for Breast Cancer dramatically affect stage-specific survival. *J Clin Oncol* 2003;21:3244-48.
- ③ 19. Fonseca R, Hartmann LC, Petersen IA, et al. Ductal carcinoma in situ of the breast. *Ann Intern Med* 1997;127:1013-22.
- ① 20. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 1999;353:1993-2000.
- ① 21. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371-88.
- ① 22. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpec-

- tomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233-41.
- ① 23. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227-32.
 - ② 24. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer: A multicenter validation study. *N Engl J Med* 1998;339:941-46.
 - ② 25. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998;16:2672-85.
 - ③ 26. www.adjuvantonline.com.
 - ① 27. Polychemotherapy for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998;352:930-42.
 - ① 28. Tamoxifen for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet* 1998;351:1451-67.
 - ② 29. Brito RA, Valero V, Buzdar AU, et al. Long-term results of combined-modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: The University of Texas M.D. Anderson Cancer Center experience. *J Clin Oncol* 2001;19:628-33.
 - ① 30. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: Long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000;88:1082-90.
 - ① 31. Nabholz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol* 2000;18:3758-67.
 - ② 32. Burstein HJ, Kuter I, Campos SM, et al. Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2001;19: 2722-30.

INTRACEREBRAL NEOPLASMS

Definition, Etiology, and Epidemiology

- More than 80%-90% of brain tumors are secondary to metastases

Primary Central Nervous System (CNS) Tumors¹

- Meningioma ~25%
- Glioma ~50%
 - Encompasses glioblastoma multiforme (GBM), astrocytoma, oligodendroglioma, and ependymoma
 - Astrocytomas are classified histologically
 - Grade I: pilocytic astrocytoma
 - Grade II: low-grade astrocytoma
 - Grade III: anaplastic astrocytoma
 - Grade IV: glioblastoma multiforme
 - GBM comprises ~25% of all primary CNS tumors
- Variety of tumor types comprise the remaining 25%

Demographics²

- Incidence of meningioma highest in elderly population; many asymptomatic
 - Female predominance
 - African American predominance
- Incidence of glioblastoma highest in late adulthood (sixth to seventh decade)
 - Male predominance
 - White predominance
- Increasing incidence of primary CNS tumors over past few decades
 - Findings limited to industrialized countries
 - Likely confounded by increased use of imaging modalities

Risk Factors

- Due to varied tumor types and wide spectrum of patient ages, identification of risk factors has been challenging
- Cellular telephone use recently demonstrated to have no causal link^{3,4}

Pearls of History and Physical Examination

History^{2,5}

- Headache
 - Most common presenting complaint
 - Often indistinguishable from tension headache
 - Can localize to side of lesion or can be diffuse
 - Exacerbation by positional change or Valsalva's maneuver
 - Worse at night and early morning
- Nausea, vomiting
- Focal neurological deficits
 - Focal weakness most common, with specific deficits based on location of lesion
- Cognitive dysfunction, personality change (typically frontal or temporal lesions)
- Focal or generalized seizures presenting complaint in up to 20% of cases
 - Up to 10% of patients with new-onset seizures have a CNS malignancy identified on imaging
 - New seizure onset in adults requires neuroimaging study to exclude mass
- Weakness, lethargy
- Decreased level of consciousness worrisome for elevated intracranial pressure (ICP)

Physical Examination

- Papilledema less commonly found on presentation as diagnosis usually made before development of increased ICP
- Evidence of elevated ICP
 - Decreased level of consciousness
 - Headache
 - Nausea/vomiting
 - Cranial nerve palsies, pupillary defects, and posturing herald herniation
 - Cushing's triad (bradycardia, hypertension, and respiratory depression) is a late finding

Diagnostic Studies and Laboratory Values

- Magnetic resonance imaging is gold standard for identifying lesions²; however, contrasted computed tomography often used as screening tool
- Positron emission tomography scans may allow differentiation of high-grade tumors (e.g., glioblastoma) from low-grade tumors (e.g., meningiomas)
- Surgical biopsy is necessary for histological diagnosis
 - Meningiomas identified incidentally on neuroimaging can be followed serially, with surgical intervention only for symptom progression

Guide to Acute Management

- General approach to acutely elevated ICP^{6,7}
 - Most studies done in traumatic brain injury; also seen in intracranial hemorrhage and large ischemic cerebrovascular accidents
 - Steroids take 48–72 hours to reduce vasogenic edema caused by tumor
 - Elevate head of bed to 30 degrees
 - Osmotic diuresis
 - Mannitol 1 g/kg IV bolus, then 0.25–0.5 g/kg every 6 hours as needed
 - Rapid effect; monitor serum sodium
 - May have additive benefit in combination with loop diuretics
 - Hyperventilation
 - Acute intervention; reduces ICP through vasoconstriction
 - Mechanically hyperventilate to P_{aCO_2} 26–30 mm Hg
 - Short-lived effect on ICP: only ~24 hours
 - Neurosurgery consult for consideration of ICP monitoring
 - Goal ICP <20 mm Hg

- Maintain cerebral perfusion pressure (CPP) > 70 mm Hg (CPP = MAP – ICP)
- Urgent/emergent surgery for biopsy and resection
- Patients with low-grade tumors (e.g., meningiomas) have good survival with neurosurgical excision alone
- Prognosis depends largely on age: 5-year survival 81% among patients younger than 65 years; 56% among patients older than 65 years⁸
- High-grade tumors often require extensive debulking for symptom control, improvement of response, adjuvant chemotherapy, and x-ray therapy
- Survival with GBM is universally poor (5-year survival 19% in children versus 0.2%-2% in adults older than 45 years)¹
- Consider referral for clinical trials

Symptomatic Therapy

- Corticosteroids
 - Standard dose is dexamethasone 10 mg bolus followed by 4 mg QID; however, some data suggest that lower doses provide similar benefit with fewer side effects⁹
- Treat documented seizures with anticonvulsants
 - No benefit of anticonvulsants for primary prophylaxis of seizures,¹⁰ except during perioperative period¹¹
- Venous thromboembolic disease
 - CNS malignancy is a high-risk hypercoagulable state
 - Risk higher than in patients with extracranial cancers; possibly related to worse functional status¹²
 - Perioperative risk is highest, but risk persists well beyond this period¹³
 - Up to 70% of patients will suffer deep vein thrombosis or pulmonary embolism
 - Aggressive prophylaxis is warranted at all times



Patient Care Warnings

- Consider CNS imaging in any patient with headache who describes a change in pattern, positional change, change with Valsalva's maneuver, or when associated with nausea and vomiting
- When intubating patients in whom increased ICP is a concern, obtaining an airway is clearly of primary importance; if possible, avoid using ketamine or succinylcholine as induction agents, as both can significantly increase ICP
- In patients on chronic steroids, be alert for development of opportunistic infections

References

- ② 1. CBTRUS (Central Brain Tumor Registry of the United States): 2002–2003 report on primary brain tumors in the United States. Chicago, Central Brain Tumor Registry of the United States, 2003.
- ③ 2. Sneed PK, Huang K, Rubenstein JL. Brain metastases and carcinomatous meningitis. In Clinical Oncology, Abeloff MD, et al. (eds). Philadelphia, Elsevier, 2004.
- ② 3. Inskip PD, Tarone RE, Hatch EE, et al: Cellular-telephone use and brain tumors. *N Engl J Med* 2001;344:79-86.
- ② 4. Muscat JE, Malkin MG, Thompson S, et al: Handheld cellular telephone use and risk of brain cancer. *J Am Med Assoc* 2000;284:3001-3007.
- ② 5. Forsyth PA, Posner JB. Headaches in patients with brain tumors: A study of 111 patients. *Neurology* 1993; 3:1678-83.
- ③ 6. Bullock R, Clifton G, et al. Guidelines for the management of severe brain injury. New York, Brain Trauma Foundation/American Association of Neurologic Surgeons, 1995.
- ③ 7. Procaccio F, Stocchetti N, Citerio G, et al. Guidelines for the treatment of adults with severe head trauma. *J Neurosurg Sci* 2000;44:1-24.
- ② 8. Palma L, Celli P, Franco C, et al. Long-term prognosis for atypical and malignant meningiomas: A study of 71 surgical cases. *J Neurosurg* 1997;86:793-800.
- ① 9. Vecht CJ, Hovestadt A, Verbiest HB, et al. Dose-effect rela-

- tionship of dexamethasone on Karnofsky performance in metastatic brain tumors: A randomized study of doses of 4, 8, and 16 mg per day. *Neurology* 1994;44:675-80.
- ② 10. Cohen N, Strauss G, Lew R, et al. Should prophylactic anticonvulsants be administered to patients with newly-diagnosed cerebral metastases? A retrospective analysis. *J Clin Oncol* 1988;6:1621-24.
 - ③ 11. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;54:1886-93.
 - ③ 12. Thoron L, Arbit E. Hemostatic changes in patients with brain tumors. *J Neurooncol* 1994;22:87-100.
 - ② 13. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: An evidence-based review. *Cancer* 2000;89:640-46.

ONCOLOGIC EMERGENCIES

Tumor Lysis Syndrome (TLS)

Definition, Etiology, and Epidemiology

- Profound tumor cell lysis with release of intracellular contents into the extracellular space
 - Characterized by a constellation of metabolic derangements, including:
 - Hyperphosphatemia
 - Hyperuricemia
 - Hypocalcemia
 - Hyperkalemia
 - Can lead to life-threatening complications, including acute renal failure (ARF) and cardiac arrhythmias
- Associated with initiation of chemotherapy in malignancies characterized by high tumor burden, high cellular turnover, and chemosensitivity¹

- Poorly differentiated (high-grade) non-Hodgkin's lymphomas
 - Burkitt's lymphoma
- Acute lymphoblastic leukemia
- Less common in acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia (blast crisis) and reported cases in multiple myeloma, breast cancer, sarcomas, germ cell tumors, and small cell lung cancer
- Spontaneous TLS (i.e., pretreatment) can rarely occur in high-grade lymphomas or acute lymphoblastic leukemia and is distinguished by lack of hyperphosphatemia (phosphate is utilized by the actively replicating tumor cells)
- Acute renal failure in TLS^{1,2}
 - Prior to use of allopurinol for TLS prophylaxis, uric acid nephropathy was most common cause of ARF (and still is in spontaneous TLS)
 - Now more commonly associated with severe hyperphosphatemia and calcium phosphate deposition in renal tubules

Pearls of the History and Physical Examination

History¹

- Nausea, vomiting, anorexia, diarrhea: caused by hyperuricemia, hyperphosphatemia and uremia
- Muscle weakness, cramps, and cardiac arrhythmias: caused by hypocalcemia and hyperkalemia
- Flank pain, hematuria, and oliguria: caused by uric acid crystal or calcium pyrophosphate deposition in renal tubules (often asymptomatic)

Physical Examination

- Assess volume status: volume depletion increases likelihood of developing renal failure

Diagnostic Studies and Laboratory Values

- Serum uric acid >15 mg/dL, serum phosphate >8 mg/dL
- High pretreatment lactic dehydrogenase levels predict severity of metabolic derangements post-treatment³
- Urinalysis often reveals acidic urine $\pm$ uric acid crystals
- Urine uric acid to urine creatinine ratio >1.0 suggests uric acid nephropathy as opposed to other causes of ARF⁴

Guide to Acute Management^{1,2,5}

- Intensive care unit or telemetry observation; baseline electrocardiogram
- Prophylaxis of TLS
 - In patients at high-risk for developing TLS, delay chemotherapy for at least 48 hours if possible to allow for allopurinol treatment and fluid loading
 - Allopurinol 600-900 mg as a single dose, followed by 300-600 mg daily to inhibit uric acid synthesis
 - Rasburicase (Elitek) 0.2 mg/kg/d for 3-7 days recently demonstrated to reduce uric acid to nearly undetectable levels in both adult and pediatric populations, even in patients with elevated pretreatment uric acid levels⁶⁻⁸
 - Recombinant urate oxidase converts uric acid to soluble allantoin
 - Used 1 day before chemotherapy or on day one
 - In 1 nonrandomized study, 0 out of 100 patients progressed to renal failure, and all maintained normal calcium, phosphate, and potassium levels
 - Intravascular volume repletion and fluid loading
 - Isotonic or hypotonic saline to maintain urine output of 2.5-3.0 L/d
 - Mannitol or loop diuretics to maintain urine output if necessary

- Marginal data regarding utility of alkalinizing urine but often employed in hopes of preventing uric acid deposition in renal tubules
 - Goal urine pH 7.1-7.5 using 1-1.5 amps of sodium bicarbonate in half normal saline
 - Avoid overalkalinization secondary to concern for accelerated calcium phosphate precipitation and worsening hypocalcemia
 - Acetazolamide 5 mg/kg/d can also be used for alkalinization of urine
- Management of TLS similar to above, with volume repletion and maintenance of urine output mainstays of therapy
 - See sections in Chapter 4 titled Hyperkalemia and Hyperphosphatemia for management of these electrolyte abnormalities
 - Unless symptomatic, avoid calcium supplementation due to risk for calcium phosphate precipitation
 - Hemodialysis may be indicated in advanced cases of TLS: specifically for volume overload, metabolic acidosis, hyperkalemia, and uremia

Superior Vena Cava (SVC) Syndrome

Definition, Etiology, and Epidemiology

- Acute or subacute obstruction of the SVC
- ~85% of cases result from extrinsic compression by malignant tumor or associated enlarged lymph nodes, occasionally caused by endovascular invasion^{9,10}
- Lung cancer is most common cause, with small cell lung carcinoma causing a disproportionately

high percentage of cases due to its predilection for central airways

- Non-Hodgkin's lymphoma is second most common cause, typically diffuse large cell or lymphoblastic subtypes; Hodgkin's disease seldom causes SVC syndrome¹¹
- Remaining malignant causes include other mediastinal tumors (e.g., germ cell tumors, thymomas) and solid tumor metastases to mediastinal lymph nodes
- Increasing proportion of cases due to indwelling lines (central venous catheters, Swan-Ganz catheter, Medi-Ports, pacemakers)¹⁰
- Fibrosing mediastinitis secondary to histoplasma, tuberculosis, or x-ray therapy (XRT) is a relatively rare cause

Pearls of the History and Physical Examination^{9,10,12}

History

- Onset and severity of symptoms are related to acuity of SVC obstruction but are typically insidious
- Dyspnea is most common complaint
- Head fullness or headache worse with supine position or lowering of head
- Arm edema, facial swelling
- Upper airway symptoms (e.g., stridor, dysphagia) are rare
- Screen for smoking history, "B" symptoms if underlying cause unknown

Physical Examination

- Dilated chest wall veins
- Elevated jugular venous pressure
- Facial edema, facial "plethora"
- Upper extremity edema
- Cyanosis is rare

Diagnostic Studies and Laboratory Values⁹

Radiographic Studies

- Chest x-ray result can be normal; however, common abnormalities include widened mediastinum, mass lesions, pleural effusions, and right upper lobe collapse
- Chest computed tomography (CT) indicated to establish diagnosis and identify most appropriate biopsy modality

Tissue Diagnosis

- Minimally invasive procedures such as sputum cytology, pleural fluid cytology, or lymph node biopsy can yield diagnosis in large proportion of cases¹³
- Bronchoscopic, mediastinoscopic, CT-guided, or open biopsy in remainder of cases

Guide to Acute Management^{9,13}

- Urgent ear, nose, and throat consultation for evidence of stridor or upper airway obstruction
- Historically, SVC syndrome managed urgently with XRT secondary to concern for rapid progression and possible neurological compromise
- Treatment deferral until tissue diagnosis confirmation does not lead to increased adverse events or progression of SVC symptoms¹³
- XRT before tissue biopsy can obscure histological diagnosis¹⁴
- Symptomatic measures include elevating head of bed and gentle diuresis
- Treatment modality depends on histological diagnosis
 - XRT alone can provide significant symptomatic relief, although addition of disease-specific chemotherapy generally provides better out-comes
 - Endovascular stenting provides marked symptomatic relief in semiurgent and palliative cases¹⁵

- Some centers are performing SVC stenting at time of initial diagnosis, with reports of improved symptoms and better tolerance of chemotherapy and XRT¹⁶

Epidural Spinal Cord Compression (ESCC)

Definition, Etiology, and Epidemiology

- Compression of thecal sac and its contents (i.e., the spinal cord or the nerve roots comprising the cauda equina) by metastatic tumor involvement of vertebral body, dura, or spinal cord
- Prostate, lung, and breast cancer each account for 15%-20% of cases^{17,18}
 - Renal cell carcinoma, multiple myeloma, and non-Hodgkin's lymphoma each account for 5%-10% of cases
- Most cases present in setting of known cancer diagnosis; however, up to 20% present as initial manifestation of malignancy¹⁹
- Metastases typically arise in the vertebral body (thoracic > cervical/lumbar) and cause compression of the spinal cord anteriorly/anterolaterally in majority of cases²⁰
- Compression of the spinal cord leads to demyelination of neurons as well as arterial and venous insufficiency, causing vasogenic edema²¹

Prognosis

- From time of diagnosis of ESCC, median survival is 6 months¹⁹
 - 9 months for radiosensitive tumors (breast, prostate, lymphoma, myeloma)
 - 3 months for lung cancer

- Functional status, specifically neurological impairment at time of diagnosis, is most important prognostic factor²²

Pearls of the History and Physical Examination^{17,18,21}

- Early detection of spinal cord compression is critical in preventing irreversible paralysis²³

History

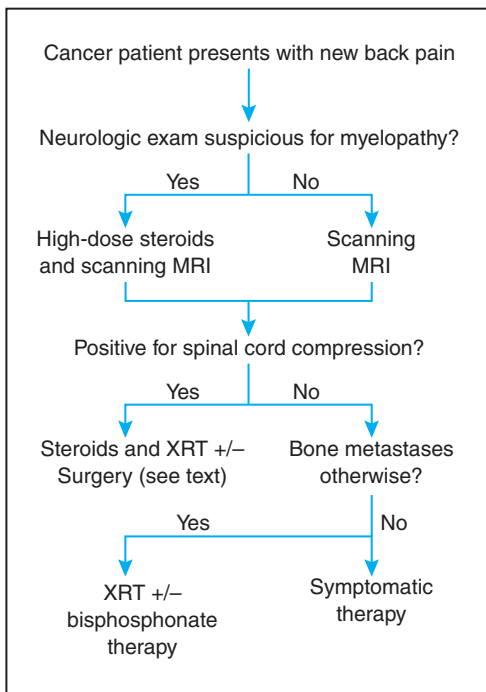
- Pain is the primary presenting complaint
- Unlike musculoskeletal back pain, pain is typically worse with recumbency and Valsalva-type maneuvers
- Pain precedes neurological compromise by only a few weeks, making early detection critical
- Loss of neurological function not required to proceed with workup
- Chronological progression of myelopathic symptoms
 - Weakness progressing to spastic or flaccid paralysis, depending on location of lesion
 - Sensory loss is often coincident with weakness
 - Ataxia
 - Bowel/bladder dysfunction (usually retention) a late finding; complete paralysis can follow within hours

Physical Examination

- Point tenderness over spine unreliable finding
- Lhermitte's sign (electric-like sensation down the spine with neck flexion) uncommonly found
- Complete neurological examination
 - Most common finding is motor weakness
 - Spasticity and hyperreflexia
 - Identifying a sensory level may suggest location of cord impingement
 - Sphincter tone
 - Palpate for bladder distention

Diagnostic Studies and Laboratory Values¹⁹

- In historical series, the majority of patients present with weakness and often paralysis; however, early detection strategies (see following figure) have made myelopathy a less frequent presenting complaint



Approach to the patient with suspected spinal cord compression. Adapted from Ruckdeschel JC. Spinal cord compression. In Abeloff MD, et al (ed). *Clinical Oncology*. Philadelphia, Elsevier, 2004.

- Any examination finding consistent with myelopathy should prompt immediate initiation of high-dose dexamethasone therapy (see below for dosing) before radiological confirmation
- Plain films, bone scans, and conventional CT scans lack sensitivity for identifying cord compression

- Diagnostic study of choice is spine magnetic resonance imaging (MRI); no need for plain films before proceeding with this
- CT myelogram for patients unable to undergo MRI

Guide to Acute Management

- Steroids, radiation therapy, and surgery are the primary therapeutic interventions
 - Patients with paraplegia lasting more than 48-72 hours are unlikely to recover cord function; therapy limited to pain control
- Minimize delay in initiating steroid therapy once ESCC is suspected
 - Adequate trial data lacking regarding optimal dosing
 - High-dose regimen (100 mg dexamethasone bolus followed by 4-10 mg QID) leads to improved neurological outcomes, but higher risk of side effects²⁴
 - No trial data to support use of standard-dose regimen (10 mg dexamethasone bolus followed by 4 mg QID); however, side effects are minimal
 - Experts recommend high-dose regimen for patients with paraparesis/paraplegia, with standard-dose regimen for those with pain only or minor neurological impairment

Radiation Therapy Versus Surgery

- XRT is mainstay of management
- Recent data support prompt surgical tumor resection followed by XRT; however, this is not standard of care at present²⁵

Symptomatic Management

- Pain control
- Aggressive use of stool softeners
- Deep vein thrombosis prophylaxis
- Wound prevention and care
- Spinal bracing may provide pain relief

Intracranial Metastases

Definition, Etiology, and Epidemiology^{26,27}

- More than 80%-90% of brain tumors are secondary to metastasis
- Primary malignancy in 40%-50% of cases is lung carcinoma
 - 15% due to breast cancer, 10% due to melanoma, and 5%-10% due to carcinoma of unknown primary
 - Other tumor types with propensity for metastasis to the brain include renal cell, colorectal, and gynecological carcinomas
- Distribution of metastases follows pattern of blood flow, typically at gray-white junction and “watershed” areas of the brain
 - 80% cerebral hemispheres, 15% cerebellar, 5% brainstem
 - Usually multiple metastatic lesions are identified
- Most cases present in setting of known cancer diagnosis; however, up to 20% present as initial manifestation of malignancy

Prognosis

- Median survival in untreated patients is 1 month
- Treatment (detailed below) can improve survival significantly, with burden of extracranial disease being the main predictor of outcome

Pearls of the History and Physical Examination^{26,27}

History

- Headache
 - Often indistinguishable from tension headache
 - Early-morning headaches and exacerbation by Valsalva’s maneuver

- Focal neurological deficit
 - Focal weakness most common, with specific deficits based on location of lesions
- Cognitive dysfunction, personality change
- Focal or generalized seizures are presenting complaint in up to 10% of cases
- Symptoms of elevated ICP are rare
- In patients with known cancer, development of altered mental status is usually due to metabolic encephalopathy and only rarely due to brain metastases

Physical Examination

- Papilledema is rare
- Motor and sensory findings are typically unilateral; bilateral symptoms should alert clinician to possibility of spinal cord compression

Diagnostic Studies and Laboratory Values

- MRI is gold standard; however, contrasted CT often used as screening tool

Guide to Acute Management

- Utility of brain biopsy limited to cases in which diagnosis of metastasis in doubt
 - Single lesion in patient with known history of cancer, but no other evidence of metastatic disease
 - Study found that, in 6 out of 54 patients, biopsy revealed a diagnosis other than metastasis²⁸
 - Solitary lesion in patient with unknown primary
 - Most likely primary is lung cancer; CT scan of chest, abdomen, and pelvis usually indicated before proceeding with surgical biopsy/excision
- Symptomatic therapy
 - Corticosteroids

- Standard dose is dexamethasone 10 mg bolus followed by 4 mg qid; however, some data suggest that lower doses provide similar benefit with fewer side effects²⁹
- Experts recommend steroid dosing based on severity of symptoms
- Corticosteroids alone extend median survival to 2 months
- Treat documented seizures with anticonvulsants
 - No benefit of anticonvulsants for primary prophylaxis of seizures³⁰
- In patients with multiple brain metastases, whole brain radiotherapy (WBRT) extends median survival to 3-6 months and improves symptoms³¹
- In patients with controlled extracranial disease and a single metastatic lesion in an accessible area, surgical resection with postoperative WBRT is superior to WBRT alone^{32,33}
- Stereotactic radiosurgery (e.g., gamma knife, cyber knife) may provide symptom control in patients who are not surgical candidates or those with multiple metastases³⁴



Patient Care Warnings

- Early detection of spinal cord compression is critical
- In patients with brain metastases or spinal cord compression, steroids are associated with significant gastrointestinal side effects; consider starting a proton pump inhibitor for prophylaxis of gastritis and peptic ulcers; steroids also increase the risk of abdominal viscus perforation and may mask clinical peritonitis

References

- ③ 1. Bishop MR, et al. Tumor lysis syndrome. In Abeloff MD, et al (ed). *Clinical Oncology*. Philadelphia, Elsevier, 2004.
- ③ 2. Arrambide K, Toto RD. Tumor lysis syndrome. *Semin Nephrol* 1993;13:273-80.
- ③ 3. Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. *Am J Med* 1993;94:133.
- ② 4. Kelton J, Kelley WN, Holmes EW. A rapid method for the diagnosis of acute uric acid nephropathy. *Arch Intern Med* 1978;138:612-15.
- ② 5. Razis E, Arlin ZA, Ahmed T, et al. Incidence and treatment of tumor lysis syndrome in patients with acute leukemia. *Acta Haematol* 1994;91:171-74.
- ① 6. Coiffier B, Mounier N, Bologna S, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: Results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. *J Clin Oncol* 2003;21:4402-4406.
- ② 7. Pui CH, Mahmoud HH, Wiley JM, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. *J Clin Oncol* 2001;19:697-704.
- ② 8. Bosly A, Sonet A, Pinkerton CR, et al. Rasburicase (recombinant urate oxidase) for the management of hyperuricemia in patients with cancer: Report of an international compassionate use study. *Cancer* 2003;98:1048-54.
- ③ 9. Laskin J, et al. Superior vena cava syndrome. In Abeloff MD, et al (ed). *Clinical Oncology*. Philadelphia, Elsevier, 2004.
- ③ 10. Escalante CP. Causes and management of superior vena cava syndrome. *Oncology* 1993;7:61-68.
- ② 11. Perez-Soler R, McLaughlin P, Velasquez WS, et al. Clinical features and results of management of superior vena cava syndrome secondary to lymphoma. *J Clin Oncol* 1984;2:260-66.
- ③ 12. Markman, M. Diagnosis and management of superior vena cava syndrome. *Cleve Clin J Med* 1999;66:59-61.
- ③ 13. Schraufnagel DE, Hill R, Leech JA, et al. Superior vena caval obstruction: Is it a medical emergency? *Am J Med* 1981;70:1169-74.
- ② 14. Loeffler JS, Leopold KA, Recht A, et al. Emergency prebiopsy radiation for mediastinal masses: Impact on subsequent pathologic diagnosis and outcome. *J Clin Oncol* 1986;4:716-21.
- ② 15. Courtheoux P, Alkofer B, Al Refai M, et al. Stent placement in superior vena cava syndrome. *Ann Thorac Surg* 2003;75:158-61.
- ② 16. Urruticoechea A, Mesia R, Dominguez J, et al. Treatment of

- malignant superior vena cava syndrome by endovascular stent insertion: Experience of 52 patients with lung cancer. *Lung Cancer* 2004;43:209-14.
- ② 17. Bach F, Larsen BH, Rohde K, et al. Metastatic spinal cord compression: Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. *Acta Neurochir (Wien)* 1990;107:37-43.
 - ② 18. Constans JP, de Divitiis E, Donzelli R, et al. Spinal metastases with neurological manifestations: Review of 600 cases. *J Neurosurg* 1983;59:111-18.
 - ② 19. Schiff D, O'Neill BP, Suman VJ. Spinal epidural metastasis as the initial manifestation of malignancy: Clinical features and diagnostic approach. *Neurology* 1997;49:452-56.
 - ② 20. Byrne TN. Spinal cord compression from epidural metastases. *N Engl J Med* 1992;327:614-19.
 - ③ 21. Ruckdeschel JC. Spinal cord compression. In Abeloff MD, et al (ed). *Clinical Oncology*. Philadelphia, Elsevier, 2004.
 - ② 22. Maranzano E, Latini P. Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: Final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 1995;32:959-67.
 - ② 23. Husband DJ. Malignant spinal cord compression: Prospective study of delays in referral and treatment. *Br Med J* 1998;317:18-21.
 - ① 24. Sorensen S, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: A randomised trial. *Eur J Cancer* 1994;30A:22-27.
 - ① 25. Patchell R, Tibbs PA, Regine WF, et al. A randomized trial of direct decompressive surgical resection in the treatment of spinal cord compression caused by metastasis [abstract]. *Proc Am Soc Clin Oncol* 2003;22:1.
 - ③ 26. Patchell RA. The management of brain metastases. *Cancer Treat Rev* 2003;29:533-40.
 - ③ 27. Sneed PK, Huang K, Rubenstein JL. Brain metastases and carcinomatous meningitis. In Abeloff MD, et al (ed). *Clinical Oncology*. Philadelphia, Elsevier, 2004.
 - ③ 28. Clouston PD, DeAngelis LM, Posner JB. The spectrum of neurological disease in patients with systemic cancer. *Ann Neurol* 1992;31:268-73.
 - ① 29. Vecht CJ, Hovestadt A, Verbiest HB, et al. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: A randomized study of doses of 4, 8, and 16 mg per day. *Neurology* 1994;44:675-80.
 - ② 30. Cohen N, Strauss G, Lew R, et al. Should prophylactic anti-convulsants be administered to patients with newly diagnosed cerebral metastases? A retrospective analysis. *J Clin Oncol* 1988;6:1621-24.
 - ③ 31. Sneed PK, Larson DA, Wara WM. Radiotherapy for cerebral metastases. *Neurosurg Clin North Am* 1996;7:505-15.
 - ① 32. Patchell RA, Tibbs PA, Walsh JW, et al: A randomized trial of

surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494-500.

- ② 33. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994;29:711-17.
- ① 34. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;363:1665-72.

EVALUATION OF ANEMIA

Definition, Etiology, and Epidemiology¹⁻³

- Defined as a decrease in red blood cell (RBC) mass as evidenced by a decrease in hemoglobin (Hgb) or hematocrit (Hct) level from normal for age and sex
- In a normal individual, anemia is defined as Hgb <12 g/dL (Hct <36%) in women and Hgb <14 g/dL (Hct <41%) in men
- Anemia can be classified based upon RBC volume

Microcytic Anemia

- Mean corpuscular volume (MCV) <80 fL
- Iron deficiency anemia: caused by blood loss, dietary deficiencies, or malabsorption
- Thalassemia shows markedly low MCV; hereditary disease results from complete absence or decreased production of alpha or beta globin chains
 - Alpha thalassemia: decreased production of alpha globin chain; severity determined by number of defective genes (four total)
 - Beta thalassemia: complete absence or decreased synthesis of beta globin chain; more common in Mediterranean, African, and Southeast Asian populations

- Anemia of chronic disease: result of inflammatory diseases (rheumatoid arthritis, infection, carcinoma, etc.)
- Sideroblastic anemia: hereditary, drugs/toxins, malignancy, collagen vascular disease, myelodysplasia variant; common pathway results in abnormal cellular uptake of iron

Normocytic Anemia

- MCV 80–100 fL
- Anemia of chronic renal disease: due to diminished production of erythropoietin
- Hemolytic anemia
 - Intrinsic causes due to defect in RBC membrane or contents
 - Hereditary spherocytosis and elliptocytosis
 - Glucose-6-phosphate dehydrogenase (G6PD) deficiency and other enzyme deficiencies
 - Sickle cell disease and other hemoglobinopathies
 - Extrinsic causes due to external factors affecting RBCs
 - Immune-mediated (autoimmune, drug-induced, infection-associated, hemolytic transfusion reaction)
 - Microangiopathic (thrombotic thrombocytopenic purpura/hemolytic uremic syndrome)
 - Infection
- Primary bone marrow disorders: aplastic anemia; drugs/toxins; radiation; bone marrow infiltrative processes, such as leukemia, lymphoma, or solid tumors

Macrocytic Anemia (MCV > 100 fL)

- Drug-induced: hydroxyurea, methotrexate, zidovudine
- Anemias associated with an elevated reticulocyte count

- Nutritional deficiencies: B₁₂, folate
- Chronic liver disease and alcoholism
- Hypothyroidism
- Myelodysplasia

Pearls of the History and Physical Examination¹⁻³

- Symptoms depend on extent of anemia and the cause and acuity of the anemic process
- Symptoms commonly arise when Hgb level falls below 7 g/dL
 - Hypovolemia: pallor, tachycardia, syncope or pre-syncope, visual impairment
 - Tissue hypoxia: headache, fatigue, dyspnea, angina
- History should focus on evidence of acute or chronic blood loss, family history of anemia, medication profile
- Physical examination should focus on evidence of pallor, jaundice, congestive heart failure, bruising or petechiae, blood loss (especially in stool), presence of lymphadenopathy, hepatic or splenic enlargement, koilonychias (“spoon nails”), and neurological signs

Diagnostic Studies and Laboratory Values

- Complete blood count including RBC indices, reticulocyte count, and evaluation of the peripheral blood smear
- Reticulocyte count represents the rate of RBC formation (i.e., number of immature RBCs as a percentage of the whole blood) and, therefore, represents the bone marrow’s ability to respond to anemia
 - Percent of reticulocytes: normal is $1.5 \pm 0.5\%$
 - Absolute reticulocyte count = percent of reticulocytes $\times$ RBC count

- Absolute reticulocyte count $>100,000/\text{mm}^3$ represents a hyperproliferative bone marrow
- Reticulocyte production index (RPI): corrects for degree of anemia and change in reticulocyte maturation time
 - $\text{RPI} = \text{percent reticulocytes} \times (\text{Hct}/45) \times 0.5$
 - Adequate marrow response: $\text{RPI} \geq 2.0$
 - Impaired marrow response: $\text{RPI} < 1.0$
- Peripheral smear should be examined for RBC shape and presence of abnormal RBC forms (e.g., schistocytes, spherocytes, teardrop cells); also look for presence or absence of platelets, abnormal leukocytes, immature forms

Microcytic Anemia¹

- Iron-deficiency anemia
 - Serum ferritin: definitive test if low; indicates iron deficiency
 - Increased red cell distribution width favors iron-deficiency anemia
 - Peripheral smear often shows microcytic, hypochromic forms with oval and pencil-shaped poikilocytes
- Thalassemia
 - B-thalassemia: diagnosis via increased HbA2
 - Peripheral smear appearances differ with the severity of the syndrome; heterozygotes have marked microcytosis, hypochromia, and target cells
- Anemia of chronic disease
 - Often decreased reticulocyte count, low serum iron, low iron binding capacity, normal or low transferrin saturation, and normal or high ferritin
- Sideroblastic anemia
 - Microcytic hypochromic RBCs; in myelodysplastic

form, smear is dimorphic; consider lead poisoning if basophilic stippling is seen on the peripheral smear

Normocytic Anemia³

- Anemia of chronic kidney disease
 - Anemia is severe with advanced kidney disease (creatinine >3 mg/dL); smear may show burr cells
 - Inappropriate erythropoietin level for the degree of anemia
- Hemolytic anemia
 - Laboratory values suggesting hemolysis include elevated lactic dehydrogenase, decreased haptoglobin, and increased indirect bilirubin levels
 - Intrinsic causes
 - Osmotic fragility test: if positive $\rightarrow$ hereditary spherocytosis
 - RBC enzyme assays: if positive $\rightarrow$ consider G6PD deficiency; check G-6-P-D in steady state
 - Sickle cell preparation: positive even in sickle trait; need hemoglobin electrophoresis for definitive assessment
 - Extrinsic causes
 - Schistocytes: presence suggests fragmentation hemolysis (valvular disease or microangiopathic process such as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome) or severe disseminated intravascular coagulation
 - Direct antiglobulin (Coombs') test: if positive, consider autoimmune hemolytic anemia; "warm" antibody has IgG, sometimes complement in direct agglutination test (DAT), and often see spherocytes on peripheral smear; "cold" antibody has complement-type DAT and agglutination on the smear
- Primary bone marrow disorder: use bone marrow evaluation

Macrocytic Anemia²

- See oval macrocytes and hypersegmented polymorphonuclear leukocytes (PMNs) in megaloblastic anemia from B₁₂ deficiency, folate deficiency, and antifolate drugs
- B₁₂ deficiency: check serum B₁₂ level; in cases of low-normal levels, check methylmalonic acid, which should be elevated in true B₁₂ deficiency
- Folate deficiency: check serum folate level
- Liver disease and hypothyroidism present as nonmegaloblastic anemia without hypersegmentation of PMNs; RBCs are usually round macrocytes

Guide to Acute Management¹⁻³

- Treatment depends on cause of the anemia:
 - Iron deficiency: identify and treat the underlying cause (thorough search for source of blood loss); iron supplementation with 65 mg of elemental iron tid; ascorbic acid given with iron to increase absorption
 - Thalassemia: depends on severity of genetic defect; may necessitate chronic transfusion, chelation therapy to avoid iron overload; heterozygote states do not need treatment, and patients should be cautioned to avoid iron, unless deficiency is confirmed
 - Anemia of chronic kidney disease: erythropoietin supplementation
 - Drug-induced anemia: discontinue offending agent
 - B₁₂ deficiency: B₁₂ 1 mg IM or SQ daily for 7 days, then weekly for 1 month, then every month
 - Folate deficiency: 1 mg folate daily



Patient Care Warnings

- Always consider active bleeding as a cause of anemia: initiate work-up before blood transfusion whenever possible
- Iron deficiency anemia should be corrected in 6–8 weeks with oral replacement, and tissue iron stores should fully recover in 6 months

References

- ③ 1. Massey A. Microcytic anemia: Differential diagnosis and management of iron deficiency anemia. *Med Clin North Am* 1992;76:549-66.
- ③ 2. Colon-Otero G, et al. A practical approach to the differential diagnosis and evaluation of the adult patient with macrocytic anemia. *Med Clin North Am* 1992;76:581-97.
- ③ 3. Tefferi A. Anemia in adults: A contemporary approach to diagnosis. *Mayo Clin Proc* 2003;78:1274-80.

PLATELET DISORDERS

Thrombocytopenia

- Platelet count less than 150,000/ μ L in the circulating blood¹
- May be artifactual, due to decreased production, increased destruction (consumptive process), or abnormal pooling and distribution¹

History and Physical Examination

- Past medical history, family history of bleeding, prescription drug use, over-the-counter medications and herbal product use, alcohol use, recent viral infections, recent transfusion, pregnancy, easy bruising

ing, vitamin B₁₂ deficiency, recent massive bleeding, or transfusion history

- Petechiae, dry or wet purpura, superficial ecchymoses, bleeding from superficial cuts, gingival bleeding, epistaxis
- Less commonly: deep hematomas
- Signs and symptoms: marked individual variation, usually present when platelet count <50,000; bleeding occurs at lower platelet counts with consumptive processes, as younger platelets function better

Clues to a Consumptive Process	Clues to a Production Problem
• Large platelets on peripheral blood smear • Signs of hemolytic anemia • Presence of other autoimmune diseases • Preceding viral infection in children • HIV	• Normal-sized platelets • Evidence of myelophthisic process of peripheral blood smear (e.g., teardrop cells, nucleated red blood cells, early white blood cell precursors) • Presence of circulating blasts • Other cytopenias suggestive of a stem cell disorder • Hypersegmented neutrophils

Modified from reference 2

Laboratory Studies

- Complete blood count and peripheral blood smear; sometimes bone marrow biopsy to assess quantity and morphology of megakaryocytes and overall marrow status; other tests as indicated

Etiology

- Pseudothrombocytopenia: clumping of platelets (can obtain platelet count in citrate instead of ethylenediaminetetraacetic acid, which usually prevents to exclude clumping⁴); of no clinical significance.

- Decreased production: aplastic anemia, myelodysplastic syndromes, acute leukemia, myelophthisis, chemotherapy/radiotherapy, thrombocytopenia and absent radius, alcohol, vitamin B₁₂ deficiency, cyclic thrombocytopenia, paroxysmal nocturnal hemoglobinuria, HIV, viral infections, medications
- Increased destruction
 - Immune-mediated
 - Idiopathic thrombocytopenic purpura (ITP): premature destruction of antibody-coated platelets in the reticuloendothelial system, especially the spleen; adults: female to male ratio 3:1⁶; usually an insidious and chronic process in adults; bleeding variable; bruising at platelet counts <30,000⁷; petechiae and overt bleeding at lower levels; splenomegaly is uncommon⁸; nonpalpable purpura (in contrast to vasculitis); in patient with isolated thrombocytopenia: normal blood smear and no splenomegaly probably do not need bone marrow biopsy⁹
 - Treatment: usually reserved for patients with platelet counts <30,000 who are undergoing procedures, or for bleeding^{12,13}; first line: prednisone 1 mg/kg¹⁴; for very low counts or significant bleeding symptoms may also use IVIG 2 g/kg over 2-5 days¹¹; failure represented by persistent thrombocytopenia (<50,000) after 3-4 weeks of prednisone or drop in platelet count to under 50,000 once prednisone is withdrawn.
 - Other treatments: dexamethasone 40 mg/d for 4 days (phase II data only);¹⁶ splenectomy 60%-70% effective for complete or partial response after failure of first-line agents¹⁷; requires presplenectomy immunizations¹⁸ for pneumococci, *Haemophilus influenza* B, and meningococci; immune blockade with anti-D 50-75 µg/kg for Rh(D)-positive patients prior to splenectomy¹⁹ (short-term efficacy only); rituximab 375 mg/m² weekly for 4 weeks produces useful rise in platelet count in 40% of refractory patients; vincristine 1-2 mg IV weekly for 4-6 weeks²⁰; cyclophos-

phamide, danazol, and Campath have also been used²¹; emergency treatment for severely bleeding patient: platelet transfusion, IV methylprednisolone, IVIG²¹

- Medications—heparin²²⁻²⁴: heparin alone can mediate platelet aggregation without antibody formation; frequency of 10%, platelets usually >100,000, onset around 48 hours, no thrombosis²³
- Heparin-induced thrombocytopenia: greater than 50% fall of platelets (5-14 days) or drop in platelet count below 100,000 secondary to antibodies directed against heparin-platelet factor-4 (PF4) complex²⁴; frequency of 1%-3%; several confirmatory tests for heparin-PF4-associated antibodies exist; treatment: stop all heparin, anticoagulation with lepirudin, argatroban, or bivalirudin with or without evidence of thrombosis²²
- Others: systemic lupus erythematosus, antiphospholipid syndrome, HIV, Ebola virus, post-transfusion purpura (rare)
- Nonimmune-mediated
 - Thrombotic thrombocytopenic purpura (TTP): requires input from hematology/oncology for this complex disorder; thrombotic microangiopathy with deficient activity of von Willebrand factor (vWF)-cleaving protease (ADAMTS13)²⁵; diagnosis: thrombocytopenia, microangiopathic hemolytic anemia (direct antiglobulin test—negative, presence of schistocytes); may not always see fever, renal failure, or mental status changes to complete classic pentad²⁶; treatment: plasma exchange (can give fresh frozen plasma prior to plasma exchange),²⁷ prednisone 1 mg/kg/d if patient fails to respond²⁸; avoid platelet transfusions
 - Others: disseminated intravascular coagulation, malignancy, eclampsia/HELLP, cardiopulmonary bypass, intra-aortic balloon pump
- Other etiologies: splenic sequestration, massive blood transfusions

Thrombocytosis

- Platelet count $>450,000$, which can be reactive or essential thrombocythemia
- Reactive causes (usually platelet count does not exceed 1,000,000): iron-deficiency anemia, asplenia/asplenic states, recovery from thrombocytopenia, malignancy, acute and chronic inflammatory and infectious diseases, exercise, medications (vincristine, epinephrine, all-trans retinoic acid), and chronic hemolytic anemia
- Blood smear review imperative as it can help differentiate between reactive and primary (essential thrombocythemia) causes; it may demonstrate iron-deficiency changes, hyposplenic changes in reactive forms, or giant and bizarre platelets in essential thrombocythemia

Qualitative Disorders of Platelets

- Inherited: von Willebrand disease, Glanzmann's thrombasthenia, Bernard-Soulier syndrome, and storage pool diseases
- Acquired: myelodysplasia, medications (especially aspirin and other antiplatelet agents), nonsteroidal anti-inflammatory agents, cephalosporins, monoclonal gammopathies

Bleeding Risks and Platelet Transfusion

- Should be based on individual patients in concordance with their clinical setting²⁹

Prophylactic Thresholds

- Acute leukemia: 10,000 (higher with fever)
- Hematopoietic cell transplantation: same as for acute leukemia
- Solid tumor: 10,000 (20,000 for aggressive therapy or necrotic tumors)

Procedure Thresholds

- Major procedure: 50,000
- Lumbar puncture: 50,000
- Endoscopy without biopsy: 50,000
- Bronchoscopy: 50,000
 - With biopsy: 70,000
- Central line placement: 50,000
- Neurosurgical procedures: 100,000
- Dental extraction: 50,000



Patient Care Warnings

- Remember that ITP is a diagnosis of exclusion
- Only the presence of hemolysis and thrombocytopenia are required to initiate plasma exchange for presumed TTP
- Transfuse platelets to the bleeding patient with thrombocytopenia, except in TTP and heparin-induced thrombocytopenia as this may exacerbate thrombosis
- Most therapy is complex; hematology/oncology consultation is recommended

References

- ③ 1. Greer JP, Foerster J, Lukens JN, et al. Wintrobe's Clinical Hematology, 11th ed. New York, Lippincott Williams & Wilkins, 2004:1529.
- ③ 2. Mazur EM. Platelets. In Schiffman FJ (ed). Hematologic Pathophysiology. Philadelphia, Lippincott-Raven, 1998:140.
- ③ 3. Drachman JG. Inherited thrombocytopenia: When a low platelet count does not mean ITP. Blood 2004;103:390.
- ③ 4. Pegels JG, Bruynes EC, von Engelfriet CP, et al. Pseudothrombocytopenia: An immunologic study on platelet antibodies dependent on ethylene diamine tetra-acetate. Blood 1982; 59:157.
- ② 5. Lusher JM, Iyer R. Idiopathic thrombocytopenic purpura in children. Semin Thromb Hemost 1977;3:175.

- ③ 6. Waters AH. Autoimmune thrombocytopenia: Clinical aspects. *Semin Hematol* 1992;29:18.
- ③ 7. George JN, Raskob GE. Idiopathic thrombocytopenic purpura: A concise summary of the pathophysiology and diagnosis in children and adults. *Semin Hematol* 1998;35:5.
- ③ 8. Doan CA, Bouroncle BA, Wiseman BK. Idiopathic and secondary thrombocytopenic purpura: Clinical study and evaluation of 381 cases over a period of 28 years. *Ann Intern Med* 1960;53:861.
- ③ 9. George JN, et al. Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996;88:3.
- ③ 10. Yang R, Zhong CH. Pathogenesis and management of chronic idiopathic thrombocytopenic purpura: An update. *Int J Hematol* 2000;71:18.
- ① 11. Jacobs P, Wood L, Novitsky N. Intravenous gammaglobulin has no advantages over oral corticosteroids as primary therapy for adults with immune thrombocytopenia: A prospective randomized clinical trial. *Am J Med* 1994;97:55.
- ③ 12. Vesely SK, Perdue JJ, Rizvi MA, et al. Management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy: A systematic review. *Ann Intern Med* 2004;140:112.
- ① 13. Cheng Y, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. *N Engl J Med* 2003;349:831.
- ② 14. McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. *Blood* 2004;104:956.
- ③ 15. CDC recommendations of the advisory committee on immunization practices: Use of vaccines and immune globulins in persons with altered immunocompetence. *Morb Mortal Wkly Rep* 1993;42:1.
- ② 16. Cooper N, et al. Does treatment with intermittent infusions of intravenous anti-D allow a proportion of adults with recently diagnosed immune thrombocytopenic purpura to avoid splenectomy? *Blood* 2002;99:1922.
- ③ 17. Berchtold P, McMillan R. Therapy of chronic idiopathic thrombocytopenic purpura in adults. *Blood* 1989;74:2309.
- ③ 18. British Committee for Standards in Haematology General Haematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children, and in pregnancy. *Br J Haematol* 2003;120:574.
- ③ 19. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: Recognition, treatment and prevention. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:311S.

- ③ 20. Brieger DB, Mak KH, Kottke-Marchant K, et al. Heparin-induced thrombocytopenia. *J Am Coll Cardiol* 1998;31:1449.
- ③ 21. Warkentin TE, et al. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. *Arch Intern Med* 2003;163:3049.
- ② 22. Veyradiaer A, et al. Specific von Willebrand factor–cleaving protease in thrombotic microangiopathies: A study of 111 cases. *Blood* 2001;98:1765.
- ③ 23. George JN. How I treat patients with thrombotic thrombocytopenic purpura–hemolytic uremic syndrome. *Blood* 2000;96:1223.
- ① 24. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med* 1991;325:393.
- ③ 25. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol* 2003;120:556.
- ③ 26. Schiffer CA, et al. Platelet transfusion for patients with cancer: Clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1519.

DISORDERS OF COAGULATION

Definition, Etiology, and Epidemiology

- Hemostasis is the process of blood clot formation and is a result of a series of interactions among endothelium, platelets, and coagulation factors
- Bleeding results from either problems with platelets or problems with coagulation factors; sometimes both occur at the same time
- Coagulation defects result from factor deficiencies, less commonly from factor inhibitors

Pearls of the History and Physical Examination

- History should focus on acute or chronic bleeding, family history of bleeding
- Petechiae and symptoms of mucosal bleeding, such

as gingival bleeding and epistaxis, are usually results of platelet dysfunction

- Symptoms of bleeding due to coagulation disorders are usually manifested as large, palpable ecchymoses and large, spreading, deep soft-tissue hematomas
- Hemarthroses are more consistent with congenital hemophilia A or B^{1,2}

Diagnostic Studies and Laboratory Values

- Evaluation of a coagulation disorder should begin with obtaining a complete blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT)
- PT measures the extrinsic pathway and common pathway¹
- aPTT measures the intrinsic and common pathway¹
- TT measures the final common step in the coagulation cascade,¹ fibrinogen to fibrin

COMMON CAUSES OF ABNORMAL COAGULATION STUDIES¹⁻³

Test Result	Etiology
Increased PT, normal PTT	Vitamin K deficiency Liver disease Coumadin therapy Early disseminated intravascular coagulation (DIC) Factor VII deficiency
Normal PT, increased PTT	Heparin use Deficiency of factors VIII, IX, XI, or XII Antiphospholipid antibodies Inhibitors of factors VIII or IX
Increased PT, increased PTT	Liver disease Coumadin or heparin use at high doses Deficiency of factors V, X, prothrombin or fibrinogen DIC Inhibitors of factors X or prothrombin (rare)

COMMON CAUSES OF ABNORMAL COAGULATION STUDIES¹⁻³ (Continued)

Test Result	Etiology
Increased TT	Hypo- or dysfibrinogenemia Monoclonal gammopathies Heparin or other thrombin inhibitor therapy

- If an abnormal coagulation test is found, a 1:1 mixing study should be performed to differentiate factor deficiency from factor inhibitors: correction with a mixing study suggests factor deficiency, failure to correct suggests the presence of an inhibitor (Note: a fairly weak inhibitor may be “flooded” by mixing with plasma, and prolonged test will correct.)³

Factor Deficiency or Inherited Disorder of Coagulation

- Hemophilia A (factor VIII deficiency)
- Hemophilia B (factor IX deficiency)
- von Willebrand disease: quantitative or qualitative disorder of von Willebrand factor, which helps to form platelet aggregates and transports factor VIII
- Factor XI deficiency
- Hypofibrinogenemia

Acquired Disorders of Coagulation

- Vitamin K deficiency: consider in patients who are malnourished, those on antibiotic therapy, and those with malabsorption syndromes
- Liver disease: leads to coagulation disorders secondary to decreased factor synthesis (von Willebrand factor and factor VIII are synthesized extrahepatically) and decreased clearance of activated clotting factors
- DIC: see low serum fibrinogen (due to consumption), elevated D-dimer and fibrin split products

- May see schistocytes on peripheral smear in severe DIC
- Consider sepsis, cancer, trauma, toxins, vascular disorders, or obstetric complications as possible etiologies
- Acquired inhibitors: molecules that directly or indirectly interfere with coagulation such as amyloid (binds factor X) and antibodies to factors VIII and IX

Guide to Acute Management

- Identify and treat underlying cause
 - Hemophilia A
 - In mild hemophilia A (VIII $\geq 5\%$), with minor bleeding, try DDAVP (0.3 $\mu\text{g}/\text{kg}$ IV or 150-300 μg intranasally) to increase the level of factor VIII
 - In severe (VIII $< 1\%$) and moderate (VIII 1%- $> 5\%$) hemophilia A, bleeding requires factor VIII replacement with purified clotting concentrate
 - Consider factor eight inhibitor bypass activity or recombinant factor VIIa for patients with inhibitors to factor VIII or IX
 - Hemophilia B: treat with purified factor IX replacement
 - von Willebrand disease
 - For minor bleeding episodes and minor surgical prophylaxis, treat with DDAVP in type 1 von Willebrand disease
 - For more serious bleeding and in types 2 and 3 von Willebrand disease, use coagulation concentrates that contain von Willebrand factor (such as Humate-P)
 - Vitamin K deficiency: oral vitamin K results in more rapid normalization of coagulation (subcutaneous [SQ] also effective); caution with intravenous therapy because of anaphylaxis risk
 - DIC: treat underlying cause; use plasma, cryoprecipitate, and platelet transfusion for patients with active bleeding

COUMADIN OVERDOSE TREATMENT ALGORITHM

INR	Bleeding Present?	Treatment
<5	No	Lower dose; omit a dose if necessary
5-9	No	Omit 1-2 doses; restart at lower dose or omit 1 dose, give 1-2.5 mg po vitamin K
>9	No	Hold coumadin, give 3-5 mg po vitamin K
>20	Serious	Hold coumadin, give 10 mg vitamin K (po or SQ)
any INR	Life-threatening	Hold coumadin, give fresh frozen plasma; give 10 mg IV vitamin K

There is a coagulation concentrate (activated prothrombin complex) that contains the vitamin K dependent factors for use in patients who cannot tolerate large volumes of plasma



Patient Care Warnings

- Management of most disorders of coagulation is complex and usually requires hematology/oncology consultation
- Always repeat abnormal coagulation studies to rule out laboratory error
- Caution when using intravenous vitamin K; may result in anaphylaxis

References

1. Suchman AL, Griner PF. Diagnostic uses of the activated partial thromboplastin time and prothrombin time. *Ann Intern Med* 1986;104:810.
2. Hoffman M. Remodeling the blood coagulation cascade. *J Thromb Thrombolysis* 2003;16:17.
3. Sahud MA. Laboratory diagnosis of inhibitors. *Semin Thromb Hemost* 2000;26:195.

TOXICITY OF COMMON CHEMOTHERAPEUTIC AGENTS

Drug	Acute Toxicity	Delayed Toxicity
<i>Alkylating Agents</i>		
Cyclophosphamide	Nausea/vomiting (N/V), hemorrhagic cystitis	Bone marrow (BM) suppression
Estramustine	N/V, diarrhea	Thrombosis, hypertension (HTN), low platelets, edema, glucose intolerance
Carmustine (BCNU), lomustine (CCNU)	N/V	Leukopenia, low platelets
Procarbazine	N/V	BM suppression, monoamine oxidase inhibitor, disulfiram-like effect
Dacarbazine	Severe N/V, anorexia	BM suppression, flu-like syndrome
Cisplatin	Severe N/V	Nephrotoxicity, neurotoxicity, BM suppression
Carboplatin	Severe N/V	Same as cisplatin but milder (preferential thrombocytopenia)
Oxaliplatin	N/V, rare anaphylactic reaction	Peripheral (cold-induced) neuropathy, BM suppression (especially thrombocytopenia), pulmonary toxicity (rare)
Chlorambucil		BM suppression
Ifosfamide	N/V, hemorrhagic cystitis, altered mental status	BM suppression

Drug	Acute Toxicity	Delayed Toxicity
Antimetabolites		
Methotrexate		BM suppression, oral and gastrointestinal (GI) ulceration, acute renal failure, hepatotoxicity, increased toxicity when effusions present, rash
Fluorouracil (5-FU)		Nausea, diarrhea, oral and GI ulceration, BM suppression, dacryocystitis
Capecitabine	Nausea, diarrhea, interaction with coumadin	Hand and foot syndrome, mucositis
Cytarabine	N/V, diarrhea, anorexia, conjunctivitis	Cystitis, N/V, BM suppression, megaloblastosis, central nervous system (CNS) toxicity
Gemcitabine	Fever, rash, N/V	BM suppression, hepatotoxicity, proteinuria
Androgens/Androgen Antagonists/ Selective Estrogen Receptor Modulators		
Testosterone propionate		Fluid retention, masculinization, leg cramps
Fluoxymesterone		Cholestatic jaundice in some; fluid retention, leg cramps
Flutamide, bicalutamide, nilutamide		Gynecomastia, hot flashes, decreased libido, hepatotoxicity,
Ethinyl estradiol		Fluid retention, feminization, uterine bleeding, gynecomastia; exacerbation of cardiovascular disease, thromboembolic disease
Tamoxifen, toremifene	Transient flare of bone pain, nausea, hot flashes, aching joints	Thromboembolic disease, anovulation, endometrial cancer, cataracts, vaginal bleeding, acne

(Continued on following page)

Drug	Acute Toxicity	Delayed Toxicity
Aromatase Inhibitors		
Anastrozole, letrozole, exemestane	Hot flushes, joint aching	Thromboembolic disease, vaginal bleeding
Pure Estrogen Receptor Antagonist		
Fulvestrant		N/V, constipation, diarrhea, abdominal pain, heart attack (H/A), back pain, hot flushes
Progestins		
Megestrol acetate	Hot flushes	Fluid retention, rare thrombosis, weight gain
Medroxyprogesterone		Same as above
GnRH Analogs		
Leuprolide	Transient flare of symptoms	Hot flushes, decreased libido, impotence, gynecomastia, nausea, diarrhea, fatigue
Adrenocorticosteroids		
Prednisone, dexamethasone	Alteration in mood	Fluid retention, HTN, diabetes mellitus, osteoporosis, gastritis, increased susceptibility to infection
Ketoconazole	Acute nausea	Gynecomastia, hepatotoxicity, adrenal insufficiency
Biological Response Modifiers		
Interferon- α 2a, 2b	Fever, chills, fatigue, anorexia	Weight loss, confusion, hypothyroidism, retinopathy, autoimmune disease
Interleukin-2	Hypotension, fever/chills, rigors, diarrhea, N/V, pruritis, capillary leak; liver, kidney, CNS toxicity	Hypoglycemia, anemia

Drug	Acute Toxicity	Delayed Toxicity
Miscellaneous		
Octreotide acetate	N/V	Diarrhea, abdominal pain, hypoglycemia
Vinblastine	N/V	Alopecia, peripheral neuropathy, BM suppression, syndrome of inappropriate antidiuretic hormone (SIADH), areflexia, constipation
Vincristine	Severe vesicant	Areflexia, peripheral neuropathy, SIADH, paralytic ileus, constipation
Vinorelbine	Mild N/V, fatigue, severe vesicant	Granulocytopenia, constipation, peripheral neuropathy, alopecia
Paclitaxel (Taxol)	Hypersensitivity reaction, mild N/V	Peripheral neuropathy, BM suppression
Taxotere	Hypersensitivity reaction, mild N/V	Fluid retention, BM suppression, neuropathy
Daunorubicin, idarubicin, doxorubicin, epirubicin	N/V	Alopecia, stomatitis, BM suppression, late cardiotoxicity (increased with radiation)
Liposomal doxorubicin, liposomal daunorubicin	Mild nausea	Hand and foot syndrome (alopecia, stomatitis, BM suppression uncommon)
Etoposide	N/V, hypotension	Alopecia, BM suppression, secondary leukemia
Mitomycin	Severe vesicant, nausea	Prolonged BM suppression, rare hemolytic uremic syndrome/thrombotic thrombocytopenic purpura

(Continued on following page)

Drug	Acute Toxicity	Delayed Toxicity
Mitoxantrone	Mild N/V	Alopecia, mild mucositis, BM suppression
Bleomycin	Allergic reactions, fever, hypotension	Fever, dermatitis, pulmonary fibrosis
Hydroxyurea	Mild N/V	Hyperpigmentation, BM suppression, macrocytosis
Miscellaneous		
Mitotane	N/V	Dermatitis, diarrhea, mental suppression, muscle tremors
Fludarabine	N/V	BM suppression, diarrhea, mild hepatotoxicity, immune suppression
Tretinoin	Retinoic acid syndrome (fever, dyspnea, pleural or pericardial effusions)	H/A, dry skin, rash, flushing
Imatinib	Mild nausea	Myalgias, edema, BM suppression, abnormal liver function test results
Rituximab	Hypersensitivity-type reactions with first infusion, fever, tumor lysis syndrome	Mild cytopenias, rare red blood cell aplasia, or aplastic anemia; severe mucocutaneous reactions (rare)
Bevacizumab	Hypertension, hypotension	Leukopenia, proteinuria
Trastuzumab	Fever, chills, N/V, arrhythmia (rare)	Hepatotoxicity
Erlotinib	Rash, fatigue, diarrhea	Interstitial lung disease (rare)
Irinotecan	Fever, diarrhea, N/V	Alopecia, BM suppression, nephrotoxicity, pulmonary toxicity
Supportive Agents		
Allopurinol		Stevens-Johnson syndrome, rash; enhances effects and toxicity of mercaptopurine

Drug	Acute Toxicity	Delayed Toxicity
Supportive Agents		
Leucovorin		Enhances toxic effects of 5-FU
Pamidronate, zoledronic acid	Symptomatic hypoglycemia (rare), flare of bone pain	Nephrotoxicity (zoledronic acid)
Epoetin- α		HTN, H/A seizures in patients on dialysis (rare)
Darbopoietin		HTN, thromboses, headache, diarrhea
Granulocyte/macrophage colony-stimulating factor	Fluid retention, dyspnea, capillary leak (rare), supraventricular tachycardia (rare), bone pain	

TRANSFUSION REACTIONS

Febrile Nonhemolytic Reaction

- Frequency: 0.12%-0.5% for red blood cell (RBC) transfusions and 1.7%-31% for platelets (if not leukocyte-reduced); 0.19% for RBC and 0.11% for platelets (if leukocyte-reduced)¹
- Etiology: cytokines from white blood cells² or plasma supernatant³, either host- or donor-released
- Signs and symptoms: $>1^{\circ}$ Celsius rise in temperature (this is a diagnosis of exclusion)⁴
- Laboratory studies: important to differentiate from hemolytic or other reactions
- Treatment: stop transfusion, exclude hemolytic reaction, antipyretics, meperidine⁵ for severe chills/rigor, leukoreduction for future transfusions¹

Acute Hemolytic Reaction

- Immune: complement-mediated via anti-RBC antibodies, usually ABO-related
- Nonimmune: from factors affecting RBC before or during infusion; related to storing and processing or conditions of infusion
- Frequency: 1:6,000-33,000; deaths in 1:500,000-800,000⁶
- Etiology: most commonly due to clerical error⁷ and failure to identify patient correctly
- Signs and symptoms: fever, chills, pain, flank pain, hypotension, renal failure (acute tubular necrosis), disseminated intravascular coagulation, hemoglobinuria
- Laboratory studies: increased lactate dehydrogenase (LDH), indirect bilirubin, plasma hemoglobin; hemoglobinuria; decreased haptoglobin
- Treatment: normal saline 100 mL/h, avoid hypotension, dopamine to maintain urine output around 100 mL/h with diuretics (furosemide) as needed^{8,9}

Delayed Hemolytic Reaction^{10,11}

- Post-transfusion finding of a positive direct antiglobulin test (DAT) and a newly developed alloantibody specificity with clinical and/or laboratory evidence of hemolysis
- Signs and symptoms: fever, jaundice, anemia, failure to match or respond to transfusion
- Laboratory studies: DAT shows IgG or complement on patient's RBCs; indirect antiglobulin test (IAT) to identify new RBC alloantibodies; evidence of hemolysis with increased LDH, decreased haptoglobin or increased indirect bilirubin
- Treatment: supportive, preventive with adequate matching; notify patients that they have an antibody

Allergic Reaction

- Urticarial reactions, rarely anaphylaxis, to blood products, usually IgE-mediated
- Frequency: 1:20,000-50,000, but IgA-deficient patients 1:9000,⁶ which can be very severe
- Etiology: IgE-mediated against anti-IgA, anti-C4, anticoagulation factors, or antihaptoglobin (Asian patients)
- Signs and symptoms: can be mild with hives, pruritis, erythema, flushing; can also be severe with stridor, wheezing, chest tightness, hypotension, cyanosis
- Laboratory studies: demonstrate the absence of hemolysis
- Treatment: epinephrine (1:1000) 0.3 mL subcutaneous or epinephrine (1:10,000) 3-5 mL intravenous if accompanied by shock⁵

Transfusion-Related Acute Lung Injury^{12,13}

- Respiratory compromise with hypoxemia requiring intervention: no other demonstrable cause
- Frequency: 1:5000 units transfused, usually within 6 hours of transfusion
- Etiology: considered to be from antileukocyte antibodies in donor plasma
- Laboratory studies: hypoxemia, pulmonary edema on chest x-ray, normal to low pulmonary capillary wedge pressure
- Treatment: supportive care including mechanical ventilation as necessary

Viral Infectious Risks With Transfusion¹⁴

- HIV 1/2: 1:2,135,000
- HCV: 1:1,935,000
- HBV: 1:205,000
- HTLV I/II: 1:2,993,000



Patient Care Warnings

- Immediately stop the transfusion if any reaction is suspected
- Febrile nonhemolytic transfusion reactions are a diagnosis of exclusion; therefore, any elevation in temperature during or after a transfusion must be taken seriously

References

- ② 1. Yazer MH, et al. The effect of prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reactions to platelet concentrates and RBC. *Transfusion* 2004;44:10-15.
- ① 2. Heddle NM, Klama L, Meyer R, et al. A randomized controlled trial comparing plasma removal with white cell reduction to prevent reactions to platelets. *Transfusion* 1999;39:231-38.
- ② 3. Muylle L, Joos M, Wouters E, et al. Increased tumor necrosis factor- α (TNF- α), interleukin-1, and interleukin-6 (IL-6) levels in the plasma of stored platelet concentrates: Relationship between TNF- α and IL-6 levels and febrile transfusion reactions. *Transfusion* 1993;33:195-99.
- ③ 4. Brecher ME, ed. Technical Manual, 14th ed. American Association of Blood Banks, Bethesda, MD, 2002.
- ③ 5. Davenport RD. Management of transfusion reactions. In Minz PD, ed. *Transfusion Therapy: Clinical Principles and Practice*. Bethesda, MD, AABB Press, 1999.
- ③ 6. DeChristopher PJ, Anderson RR. Risks of transfusion and organ and tissue transplantation: Practical concerns that drive practical policies. *Am J Clin Pathol* 1997;107(Suppl 1):S2-11.
- ② 7. Sazama K. Reports of 355 transfusion-associated deaths: 1976 through 1985. *Transfusion* 1990;30:583-90.
- ③ 8. Anstall HB, Blaylock RC. Adverse reactions to transfusion: Part I. In *Practical Aspects of the Transfusion Service*. Chicago, ASCP Press, 1996.
- ③ 9. Goldfinger D. Acute hemolytic transfusion reactions: A fresh look at pathogenesis and considerations regarding therapy. *Transfusion* 1977;17:85-98.
- ② 10. Ness PM, Shirey RS, Thoman SK. The differentiation of delayed serologic and delayed hemolytic transfusion reactions: Incidence, long-term serologic findings, and clinical significance. *Transfusion* 1990;30:688-93.

- ③ 11. Vengelen-Tyler V. AABB Technical Manual, 13th ed. Bethesda, MD, AABB Press, 1999.
- ③ 12. Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985;25:573-77.
- ② 13. Silliman CC, Lynn K, Boshkov ZM, et al. Transfusion-related acute lung injury: Epidemiology and a prospective analysis of etiologic factors. *Blood* 2003;101:454-62.
- ③ 14. Pomper GJ, Wu Y, Snyder EL. Risks of transfusion-transmitted infections: 2003. *Curr Opin Hematol* 2003;10:412-18.
- ③ 15. Goodnough LT, Brecher ME, Kanter MH, et al. Medical progress: Transfusion medicine: Blood transfusion. *N Engl J Med* 1999;340:438-47.
- ③ 16. Hillyer CD, Hillyer KL, Strobl FJ, et al. *Handbook of Transfusion Medicine*. San Diego, Academic Press, 2001.

MYELODYSPLASTIC AND MYELOPROLIFERATIVE DISORDERS

Myelodysplastic Syndrome (MDS)

Definition, Etiology, and Epidemiology¹⁻³

- Clonal stem cell disorder characterized by dysplastic hematopoiesis and peripheral cytopenias
- < 20% bone marrow blast cells
- Therapy-related MDS can occur 3-7 years following treatment with alkylating (e.g., cyclophosphamide) agents, topoisomerase II inhibitors (e.g., doxorubicin and etoposide), chemoradiation, or total body irradiation
- Most common hematological malignancy occurs in patients older than 60 years, approximately 4 cases/100,000 people per year
- Approximately 25% transformation to acute myelogenous leukemia (AML)
- World Health Organization Classifications

- Refractory anemia (RA)
- RA with ringed sideroblasts
- Refractory cytopenia with multilineage dysplasia
- RA with excess blasts
- Unclassifiable MDS
- 5q-syndrome

Pearls of the History and Physical Examination¹⁻³

- Predisposing conditions: increasing age (>50 years old)
- Evaluate for symptoms related to cytopenia
- Morbidity and mortality rates are most likely secondary to anemia and infections

Physical Examination Findings³

- Pallor (60%)
- Easy bruising (petechiae, purpura), mucosal bleeding
- Infections (mostly bacterial, skin)

Diagnostic Studies and Laboratory Values¹⁻³

- Chromosome deletions (5q-, monosomy 7)
- Rule out other causes of peripheral blood cytopenias

Complete Blood Count

- Peripheral anemia (normocytic or macrocytic)
- Neutropenia ($\pm$ pseudo-Pelger-Huet anomaly/hyposegmented neutrophils)
- Thrombocytopenia (although thrombocytosis is possible in 5q- syndrome)

Bone Marrow Biopsy

- Hypercellularity > hypocellularity (<30%)
- Aspirate
- Iron stains: look for ringed sideroblasts
- Cytogenetics

Guide to Acute Management²⁻⁴

- Mostly supportive therapy: transfusion of leukoreduced red blood cells (RBCs) and platelets, antibiotics for infection, hematopoietic growth factors (erythropoietin and granulocyte colony-stimulating factor)
- Treatment individualized based on age, subtype, and International Prognostic Scoring System (IPSS: % bone marrow blasts, cytogenetics, cytopenias); options include hypomethylating agents (5-azacytidine, decitabine), lenalidomide (5q-)
- Allogeneic hematopoietic cell transplantation in younger patients with HLA-compatible donor or poor prognosis
- Recommend enrollment in clinical trials

Chronic Myeloproliferative Disorders (CMPD)

Definition, Etiology, and Epidemiology

- Clonal stem cell disorders characterized by peripheral mature myeloid cell expansion
- The classic CMPDs are chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and chronic idiopathic myelofibrosis (IMF)
- Phenotypic overlap in CMPD
- Each group has incidence of 1.5-2.5 per 100,000 people per year⁵⁻⁸
- Median age is 55-65 years⁵⁻⁸
- Transformation to AML occurs more frequently and with less time in CML (>90% over several years)

than with the other CMPDs (PV $\leq$ 25%, ET $\leq$ 5% over decades)⁵⁻⁸

- CML: Philadelphia chromosome t(9;22) giving rise to Bcr-Abl tyrosine kinase
- PV: Erythrocytosis (elevated RBC mass; 20% isolated and 40% trilineage hyperplasia)
- ET: Diagnosis of exclusion; nonreactive persistent isolated thrombocytosis with platelet count $>600,000/\mu\text{L}$; normal life expectancy
- IMF: Bone marrow fibrosis, osteosclerosis and angiogenesis; increased CD34+ cells; worst survival (median 5 years) among all CMPDs

Pearls of the History and Physical Examination

- Predisposing conditions: increasing age, ionizing radiation (CML)

Chronic Myelogenous Leukemia⁵

- Triphasic course: chronic (~5 years), accelerated (~6 months), and blast (~3 months) phases
- Systemic malaise, diaphoresis, weight loss
- Fatigue (seen with anemia)
- Thrombosis (especially age >60 years)
- Splenomegaly (~60%, left upper quadrant [LUQ] abdominal pain)
- Bone pain due to extramedullary hematopoiesis
- Acute gouty arthritis (hyperuricemia)
- Pallor due to anemia
- Hepatomegaly (20%)

Polycythemia Vera⁶

- Aquagenic pruritis (40%): pruritus on exposure of skin to warm water
- Microvascular occlusions (headache, erythromelalgia: treated with aspirin)
- Morbidity and mortality rates mostly secondary to

thrombohemorrhagic complications; may see both arterial and venous thrombosis (i.e., Budd-Chiari syndrome)

- Splenomegaly (80%)

Essential Thrombocythemia⁷

- Microvascular occlusions (erythromelalgia, livedo reticularis, headache)
- Morbidity and mortality rates mostly secondary to thrombohemorrhagic complications; may see both arterial and venous thrombosis
- Bleeding can occur if platelets >1 million (pseudo-von Willebrand syndrome)
- Splenomegaly (40%)

Idiopathic Myelofibrosis⁸

- Hypercatabolic state (fever, fatigue, night sweats, weight loss)
- Morbidity and mortality rates mostly secondary to anemia and massive splenomegaly (with associated LUQ pain, portal hypertension)
- Bone pain may be present due to marrow fibrosis
- Extramedullary hematopoiesis may involve any organ

Diagnostic Studies and Laboratory Values

Chronic Myelogenous Leukemia⁵

- Cytogenetics on bone marrow of peripheral blood to detect Philadelphia chromosome or Bcr-Abl tyrosine kinase
- Neutrophilic leukocytosis (white blood cells >100K, 60%) with absolute basophilia and eosinophilia, anemia (50%)
- Thrombocytosis (platelets >600K, 40%)
- Hyperuricemia
- Monocytosis (*p190 Bcr-Abl*)

***Polycythemia Vera*⁶**

- PV support group diagnostic criteria (need three major criteria, or first two major criteria with two minor criteria)
 - Major
 - Erythrocytosis: RBC mass >36 mL/kg (male), >32 mL/kg (female) (corresponds to Hct $>56\%$ [male] and Hct $>50\%$ [female], although this does not form part of the criteria and no consensus on Hct values has been reached)
 - Arterial O₂ saturation $>92\%$
 - Splenomegaly
 - Minor
 - Thrombocytosis $>400,000$
 - Leukocytosis $>12,000$ in absence of infection
 - Leukocyte alkaline phosphatase >100 in absence of infection
 - Vitamin B₁₂ >900 pg/mL
- Serum erythropoietin level (low $>$ normal)
- Bone marrow hypercellularity with increased megakaryocytes and decreased iron stores $\pm$ myelofibrosis (12%)

***Essential Thrombocythemia*⁷**

- Persistent platelet counts $>600,000/\mu\text{L}$
- Bone marrow megakaryocytic hyperplasia
- No iron deficiency or inflammation (normal serum ferritin, mean corpuscular volume, C-reactive protein, and IL-6 levels)
- Exclusion of other CMPDs, other causes of reactive thrombocytosis (malignancy, anemia, infection, inflammatory processes), and MDS (5q- syndrome)

***Idiopathic Myelofibrosis*⁸**

- Peripheral blood myelophthisis (leukoerythroblasts, teardrop-shaped RBCs, nucleated RBCs)
- Splenomegaly by imaging

- Exclusion of other CMPDs, MDS, and other causes of myelofibrosis (malignancy, autoimmune disorders, renal osteodystrophy)

Guide to Acute Management

Chronic Myelogenous Leukemia⁵

- Younger patients (<50 years) with matched related donor: allogeneic hematopoietic cell transplant (HCT); need to balance transplant risk versus nontransplant prognosis (long-term outcome with Gleevec not yet known)
- Older patients (>60 years): treat with imatinib (Gleevec)
- Patients 50-60 years: allogeneic HCT versus imatinib; second line is interferon- α (INF- α)/cytarabine (although studies indicate better cytogenetic response with imatinib)^{9,10}
- Increased concern for progression to acute leukemia versus thrombotic complications in younger and older patients, respectively
- Palliation with chemotherapy (hydroxyurea > busulfan)

Polycythemia Vera⁶

- Erythrocythemia: periodic phlebotomy to hematocrit level $\leq 45\%$ (male), $\leq 42\%$ (female)
- Thrombosis
 - Low-risk: treat with aspirin ≤ 100 mg/d
 - High-risk: hydroxyurea or busulfan; IFN- α in pregnancy; consider³²P if life expectancy <10 years
- Pruritus
 - Generalized: treat with paroxetine
 - Intractable: treat with IFN- α

Essential Thrombocythemia⁷

- Asymptomatic: observe patient
- Thrombosis

- Low-risk (i.e., no high-risk factors, platelet count <1.5 million/ μL , and no cardiovascular risk factors): treat with aspirin ≤ 325 mg/d
- High-risk (age >60 years, prior history of thrombosis): treat with anagrelide or hydroxyurea; IFN- α in pregnancy; goal = platelet count around 400,000
- Avoid nonsteroidal anti-inflammatory drugs and aspirin at levels >325 mg/d

Idiopathic Myelofibrosis⁸

- Anemia: treat with erythropoietin; can try thalidomide, interferon;^{11,12} supportive therapy with leukoreduced RBC transfusions
- Splenomegaly: hydroxyurea; splenectomy if refractory or high transfusion requirement¹³
- Low-dose splenic radiation for splenomegaly due to extramedullary hematopoiesis
- Consider allogeneic hematopoietic cell transplant in younger patients with poor prognosis¹⁴



Patient Care Warnings

- In MDS, bleeding may occur even with adequate platelet counts due to platelet dysfunction: consider prophylactic platelet transfusions prior to surgical procedures
- Phenotypic overlap in CMPDs complicates appropriate diagnosis and treatment
- Hydroxyurea may have leukemogenic potential, especially with prior exposure to alkylating agent; should be used with caution in younger patients

References

- ③ 1. Brunning RD, Bennett JM, Flandrin G, et al. Myelodysplastic syndromes. In Jeffe ES, Harris NL, Stein H, et al (eds). WHO Classification of Tumors: Pathology and Genetics: Tumours of Hematopoietic and Lymphoid Tissues, 2002:62-73.
- ③ 2. Valent R, Wimazal F, Schwarzeninger I, et al. Pathogenesis, classification and treatment of myelodysplastic syndromes (MDS). *Wien Klin Wochenschr* 2003;115:515-36.
- ③ 3. Langston AA, Walling R, Winton EF. Update on myelodysplastic syndromes: New approaches to classification and therapy. *Semin Oncol* 2004;31(Suppl 4):72-79.
- ③ 4. Faderl S, Kantarjian HM. Novel therapies for myelodysplastic syndromes. *Cancer* 2004;101:226-41.
- ③ 5. Goldman JM. Therapeutic strategies for chronic myeloid leukemia in the chronic (stable) phase. *Semin Hematol* 2003;40(Suppl 1):10-17.
- ③ 6. Tefferi A. Polycythemia vera: A comprehensive review and clinical recommendations. *Mayo Clin Proc* 2003;78:174-94.
- ③ 7. Barbui T. Indications for lowering platelet numbers in essential thrombocythemia. *Semin Hematol* 2003;40(Suppl 1):22-25.
- ③ 8. Tefferi A. Treatment approaches in myelofibrosis with myeloid metaplasia: The old and the new. *Semin Hematol* 2003;40(Suppl 1):18-21.
- ① 9. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;348:994-1002.
- ② 10. Hahn EA, Glendenning GA, Sorensen MV, et al. Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alpha plus low-dose cytarabine: Results from the IRIS study. *J Clin Oncol* 2003;21:2138-46.
- ② 11. Elliott MA, Mesa RA, Li CY, et al. Thalidomide treatment in myelofibrosis with myeloid metaplasia. *Br J Haematol* 2002;117:288-96.
- ① 12. Marchetti M, Barosi G, Balestri F, et al. Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: A phase II trial. *J Clin Oncol* 2004;22:424-31.
- ② 13. Tefferi A, Mesa RA, Nagorney DM, et al. Splenectomy in myelofibrosis with myeloid metaplasia: A single-institution experience with 223 patients. *Blood* 2000;95:2226-33.
- ② 14. Deeg HJ, Gooley TA, Flowers ME, et al. Allogeneic hematopoietic stem cell transplantation for myelofibrosis. *Blood* 2003;102:3912-18.

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SELECTED DIFFERENTIAL DIAGNOSES FOR COMMON SIGNS AND SYMPTOMS

Sign/Symptom	Differential Diagnosis	Section Title
Cardiology		
Acute chest pain	Myocardial ischemia/infarction	Ischemic Heart Disease
	Pericarditis	Pericarditis
		Pericardial Effusions
	Aortic dissection	Aortic Dissection
	Pneumothorax	Differential Diagnoses in Thoracic Radiology
	Pneumonia	Pneumonia; Nosocomial Pneumonia
	Pulmonary embolism	Venous Thromboembolism
	Gastroesophageal reflux	Esophageal Disorders
	Esophageal rupture/spasm	Esophageal Disorders
	Esophagitis	Esophageal Disorders
Sinus tachycardia	Musculoskeletal chest wall pain	
	Mediastinitis	
	Fever	Fever and Leukocytosis in the ICU; Fever of Unknown Origin; Neutropenic Fever; Pneumonia; Nosocomial Pneumonia; Meningitis/Encephalitis; Cellulitis, Necrotizing Fasciitis, Subcutaneous Abscess and Osteomyelitis; Sepsis; Management of

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Sign/Symptom	Differential Diagnosis	Section Title
Cardiology (<i>continued</i>)		
		Tuberculosis; PCP and Other HIV-Related Pulmonary Disease; Immune Reconstitution Syndrome; Acute Retroviral Syndrome; Sepsis; Inflammatory Bowel Disease; Mesenteric Ischemia; Acute and Chronic Diarrhea; Pancreatitis; Fulminant Hepatic Failure; Spontaneous Bacterial Peritonitis; Biliary Disease; Acute Viral Hepatitis; Infective Endocarditis; Pericarditis
	Hypovolemia	
	Left ventricular dysfunction	Congestive Heart Failure and Systolic Dysfunction
	Sepsis	Sepsis
	Thyrotoxicosis	Thyroid Disease
	Adrenal insufficiency	Adrenal Insufficiency
	Hypoxia	Pneumonia; Nosocomial Pneumonia; Venous Thromboembolism; PCP and Other HIV-Related Pulmonary Disease; Pleural Effusions; Chronic Obstructive Lung Disease; The Other Obstructive Lung Diseases; ARDS; Pulmonary Hypertension; Hepatorenal and Hepatopulmonary Syndromes
	Pulmonary embolism	Venous Thromboembolism
	Pericardial effusion ± tamponade	Pericardial Effusions; Pericarditis; Indications for Emergent Echocardiography

Sign/Symptom	Differential Diagnosis	Section Title
Sinus bradycardia	Anemia	Evaluation of Anemia
	Pain	
	Hypothermia	
	Hypothyroidism	Thyroid Disease
	Sick sinus syndrome	Bradyarrhythmia; High-Yield ECG Findings
	Complication of myocardial infarction	Complications Following Myocardial Infarction
	Infiltrative cardiomyopathy	Congestive Heart Failure and Systolic Dysfunction; Diastolic Dysfunction, Restrictive Cardiomyopathy, Constrictive Pericarditis, and Hypertrophic Cardiomyopathy
	Increased intracranial pressure	Intracranial Hemorrhage; Hypertensive Crises; Intracerebral Neoplasms; Oncologic Emergencies; Acute Liver Failure; Meningitis/Encephalitis
	Medication/drug toxicity	Toxidromes
	Heart block	Bradyarrhythmia; High-Yield ECG Findings; Complications Following Myocardial Infarction; Infective Endocarditis
Acute heart failure	Myocardial ischemia/infarction	Ischemic Heart Disease
	Hypertension	Hypertensive Crises
	Acute mitral regurgitation	Mitral Stenosis and Regurgitation; Infective Endocarditis
	Acute aortic insufficiency	Aortic Stenosis and Regurgitation; Infective Endocarditis
	Myocarditis	Congestive Heart Failure and Systolic Dysfunction;

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Sign/Symptom	Differential Diagnosis	Section Title
Cardiology (continued)		
		Diastolic Dysfunction, Restrictive Cardiomyopathy, Constrictive Pericarditis, and Hypertrophic Cardiomyopathy; Inflammatory Myopathies
	High output heart failure	Congestive Heart Failure and Systolic Dysfunction; Thyroid Disease; Evaluation of Anemia
	Medication/drug toxicity	Toxidromes
	Arrhythmia	High-Yield ECG Findings; Narrow Complex Tachycardia; Wide Complex Tachycardia; Bradyarrhythmia; Complications Following Myocardial Infarction
Precipitants of decompensation in chronic heart failure	Medication/drug toxicity	Toxidromes
	Medication non-compliance	
	Increased salt intake	
	Valvular heart disease	Aortic Stenosis and Regurgitation; Mitral Stenosis and Regurgitation; Tricuspid Stenosis and Regurgitation; Infective Endocarditis; Complications Following Myocardial Infarction
	Renal failure	Acute Renal Failure
	Hypertension	Hypertensive Crises
	Arrhythmias	High-Yield ECG Findings; Narrow Complex Tachycardia; Wide Complex

Sign/Symptom	Differential Diagnosis	Section Title
Right heart failure		Tachycardia; Bradycardia; Complications Following Myocardial Infarction
	Device malfunction	Pacemakers and Defibrillators
	Left ventricular dysfunction	Congestive Heart Failure and Systolic Dysfunction
	Parenchymal lung disease	Interstitial Lung Disease
	Obstructive lung disease	Chronic Obstructive Lung Disease; The Other Obstructive Lung Diseases
	Pulmonary embolism	Venous Thromboembolism
	Primary or secondary pulmonary hypertension	Pulmonary Hypertension
	Right ventricular infarction	Ischemic Heart Disease
	Valvular dysfunction	Tricuspid Stenosis and Regurgitation; Mitral Stenosis and Regurgitation; Aortic Stenosis and Regurgitation
	Infiltrative cardiomyopathy	Congestive Heart Failure and Systolic Dysfunction; Diastolic Dysfunction, Restrictive Cardiomyopathy, Constrictive Pericarditis, and Hypertrophic Cardiomyopathy
	Pericardial effusion $\pm$ cardiac tamponade	Pericarditis; Pericardial Effusions; Indications for Emergent Echocardiography
Atrial fibrillation	Myocardial ischemia/infarction	Ischemic Heart Disease; Complications Following Myocardial Infarction

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Sign/Symptom	Differential Diagnosis	Section Title
Syncope	Cardiology (<i>continued</i>)	
	Pericarditis	Pericarditis; Pericardial Effusions
	Thyrotoxicosis	Thyroid Disease
	Pain	
	Infection, sepsis	Sepsis
	Volume overload	Congestive Heart Failure and Systolic Dysfunction; Acute Renal Failure
	Alcohol use/withdrawal	Toxidromes
	Medication/drug toxicity	Toxidromes
	Valvular heart disease	Mitral Stenosis and Regurgitation; Tricuspid Stenosis and Regurgitation
	Structural heart disease	Congestive Heart Failure and Systolic Dysfunction
	Atrial and ventricular arrhythmias	High-Yield ECG Findings; Narrow Complex Tachycardia; Wide Complex Tachycardia; Bradyarrhythmia; Atrial Fibrillation and Flutter
	Heart block	Bradyarrhythmia; Infective Endocarditis; Complications Following Myocardial Infarction
	Sinus bradycardia	Bradyarrhythmia; Complications Following Myocardial Infarction
	Increased vagal tone	Syncope
	Carotid body hypersensitivity	Syncope
	Volume depletion/orthostasis	
	Vasodilatory drugs	Critical Care Pharmacology
	Aortic stenosis	Aortic Stenosis and Regurgitation

Sign/Symptom	Differential Diagnosis	Section Title
Prolonged QT-interval	Hypertrophic cardiomyopathy with outflow obstruction	Diastolic Dysfunction, Restrictive Cardiomyopathy, Constrictive Pericarditis, and Hypertrophic Cardiomyopathy
	Autonomic dysfunction	
	Hypokalemia	Hypokalemia
	Hypocalcemia Hypomagnesemia Medication/drug toxicity	Calcium Homeostasis Hypomagnesemia Toxidromes
	Increased intracranial pressure	Intracranial Hemorrhage; Hypertensive Crises; Intracerebral Neoplasms; Oncologic Emergencies; Acute Liver Failure
Tall R-wave in lead V1	Familial syndromes	
	Right bundle branch block	High-Yield ECG Findings
	Right ventricular hypertrophy	
	Right ventricular strain	Venous Thromboembolism; Pulmonary Hypertension
	Posterior wall infarction	Ischemic Heart Disease; Complications Following Myocardial Infarction; High-Yield ECG Findings
Widened pulse pressure	Wolf-Parkinson White syndrome	Narrow Complex Tachycardia; High-Yield ECG Findings; Indications for Electrophysiological (EP) Testing
	Aortic insufficiency Sepsis	Aortic Stenosis and Regurgitation Sepsis

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Sign/Symptom	Differential Diagnosis	Section Title
Cardiology <i>(continued)</i>		
	Thyrotoxicosis	Thyroid Disease
	Pregnancy	
	Atrioventricular fistula	
	Beri-beri	
	Paget's disease	
Pulmonology		
Hypoxia	Pulmonary embolism	Venous Thromboembolism
	Chronic obstructive pulmonary disease	Chronic Obstructive Pulmonary Disease
	Atelectasis	
	Consolidation	Differential Diagnoses in Thoracic Radiology
	Atrial septal defect	
	Ventricular septal defect	Complications Following Myocardial Infarction
	Acute respiratory distress syndrome	Acute Respiratory Distress Syndrome (ARDS)
	Cardiogenic or noncardiogenic pulmonary edema	Differential Diagnoses in Thoracic Radiology; Congestive Heart Failure; ARDS
	Hypoventilation	
	Carbon monoxide poisoning	
	Low inspired oxygen concentration	
	Pneumonia	Pneumonia; Nosocomial Pneumonia; PCP and Other HIV-Related Pulmonary Diseases; Management of Tuberculosis

Sign/Symptom	Differential Diagnosis	Section Title
Hypoventilation	Hepatopulmonary syndrome	Hepatorenal and Hepatopulmonary Syndromes
	Decreased central respiratory drive	
	Medication/sedative effect	Toxidromes
	Ingestion/ethanol toxicity	Toxidromes
	Hypoglycemia	
Hyperventilation	Neuromuscular disease	
	Kyphoscoliosis	
	Fatigue	
	Metabolic alkalosis	Acid-Base Disorders
	Pain	
Hemoptysis	Anxiety	
	Increased intracranial pressure	Intracranial Hemorrhage; Hypertensive Crises; Intracerebral Neoplasms; Oncologic Emergencies; Acute Liver Failure
	Metabolic acidosis	Acid-Base Disorders
	Hypoxia	
	Salicylate toxicity	Toxidromes
Hemoptysis	Pregnancy	
	Nose bleed	
	Bronchitis	
	Bronchiectasis	The Other Obstructive Lung Diseases; Evaluation of Hemoptysis
	Pneumonia	Pneumonia, Nosocomial Pneumonia; Evaluation of Hemoptysis
	Lung abscess	
	Pulmonary embolism with infarct	Venous Thromboembolism; Evaluation of Hemoptysis

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Sign/Symptom	Differential Diagnosis	Section Title
Pulmonology <i>(continued)</i>		
	Tuberculosis	Management of Tuberculosis; Evaluation of Hemoptysis
	Fungal infection	Pneumonia; Nosocomial Pneumonia
	Vasculitis	Large Vessel Vasculitis; Small Vessel Vasculitis; Evaluation of Hemoptysis
	Arteriovenous malformations	Lung Cancer
	Bronchogenic carcinoma	
	Bronchial artery bleed	
	Alveolar hemorrhage	Systemic Lupus Erythematosus; Evaluation of Hemoptysis; Indications for Emergent Bronchoscopy
	Bleeding diathesis	Disorders of Coagulation; Platelet Disorders; Evaluation of Anemia
	Mitral stenosis	Mitral Stenosis and Regurgitation
Upper airway obstruction	Angioedema	
	Foreign body aspiration	Indications for Emergent Bronchoscopy
	Mediastinal neoplasm	Lung Cancer; Hodgkin's Disease; Non-Hodgkin's Lymphoma; Breast Cancer; Oncologic Emergencies
	Head and neck cancer	
	Retropharyngeal abscess	
	Laryngomalacia	
	Epiglottitis	

Sign/Symptom	Differential Diagnosis	Section Title
Acute dyspnea	Vocal cord paralysis/dysfunction	
	Postextubation inflammation	
	Pulmonary edema	Congestive Heart Failure and Systolic Dysfunction; Diastolic Dysfunction, ARDS
	Pulmonary embolism	Venous Thromboembolism
	Pneumothorax	Differential Diagnoses in Thoracic Radiology
	Chronic obstructive pulmonary disease	Chronic Obstructive Pulmonary Disease
	Asthma	The Other Obstructive Lung Diseases
Acute respiratory distress syndrome	Pneumonia	Pneumonia; Nosocomial Pneumonia; PCP and Other HIV-Related Pulmonary Diseases
	Hyperventilation	
	Metabolic acidosis	Acid-Base Disorders
	Acute respiratory distress syndrome	Acute Respiratory Distress Syndrome
	Sepsis	Sepsis
	Pneumonia	Pneumonia; Nosocomial Pneumonia; HIV and its Complications; PCP and Other HIV-Related Pulmonary Diseases
	Aspiration	
	Alveolar hemorrhage	Evaluation of Hemoptysis; Indications for Emergent Bronchoscopy
	Transfusion-related lung injury	Transfusion Reactions

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Sign/Symptom	Differential Diagnosis	Section Title
Pulmonology <i>(continued)</i>		
Clubbing	Acute interstitial pneumonitis	Interstitial Lung Disease; Acute Respiratory Distress Syndrome
	Pancreatitis	Pancreatitis
	Burn injury	
	Fat emboli	Acute Respiratory Distress Syndrome
	Medication/drug toxicity	Toxidromes
	Bronchogenic carcinoma	Lung Cancer
	Bronchiectasis	The Other Obstructive Lung Diseases
	Asbestosis	
	Pulmonary fibrosis	Interstitial Lung Disease
	Endocarditis	Infective Endocarditis
	Congenital heart disease	
	Inflammatory bowel disease	Inflammatory Bowel Disease
Nephrology		
Hematuria	Cirrhosis	Abnormal Liver Function Tests; Acute Viral Hepatitis; Acute Liver Failure; Ascites
	Cystitis	
	Bladder diverticuli	
	Bladder/urethral trauma	
	Bladder malignancy	
	Urethritis	
	Prostatitis	
	Prostate cancer	Prostate Cancer
	Nephrolithiasis	
	Renal/ureteral malignancy	
	Renal infarction	

Sign/Symptom	Differential Diagnosis	Section Title
Proteinuria	Renal vein thrombosis	Acute Renal Failure
	Renal cyst with hemorrhage	
	Pyelonephritis	
	Papillary necrosis	Acute Renal Failure
	Glomerulonephritis	
	IgA nephropathy	Acute Renal Failure
	Thin basement membrane disease	Acute Renal Failure
	Diabetes mellitus	Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State; Acute Renal Failure
	Multiple myeloma	Multiple Myeloma and Other Plasma Cell Dyscrasias
	Amyloidosis	Multiple Myeloma and Other Plasma Cell Dyscrasias
Myoglobinuria	Membranous glomerulonephropathy	Acute Renal Failure
	Focal segmental glomerulosclerosis	Acute Renal Failure
	Minimal change disease	Acute Renal Failure
	Membranoproliferative disease	Acute Renal Failure
	Lupus nephritis	Acute Renal Failure; Systemic Lupus Erythematosus
	Medication/drug toxicity	Toxidromes
	Postexercise	
	Burn and thermal injury	Toxidromes
	Heat stroke	

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Sign/Symptom	Differential Diagnosis	Section Title
Nephrology (<i>continued</i>)		
	Crush injury, compartment syndrome	
	Status epilepticus	Seizures
	Delirium tremens	Toxidromes
	Hypophosphatemia	Hypophosphatemia
	Hypomagnesaemia	Hypomagnesaemia
Anion-gap acidosis	Ketoacidosis	Acid-Base Disorders; Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State
	Renal failure	Acute Renal Failure
	Salicylate toxicity	Toxidromes; Acid-Base Disorders
	Methanol ingestion	Toxidromes; Acid-Base Disorders
	Acetaldehyde ingestion	Acid-Base Disorders
	Ethylene glycol ingestion	Toxidromes; Acid-Base Disorders
	Lactic acidosis	Acid-Base Disorders
	Metformin-associated lactic acidosis	Acid-Base Disorders
	Isoniazid use	Acid-Base Disorders; Management of Tuberculosis
	Antiretroviral use (lamivudine)	HIV and Its Complications; Immune Reconstitution Syndrome
Nonanion gap acidosis	Diarrhea	Acute and Chronic Diarrhea
	Gastrointestinal fistula	Inflammatory Bowel Disease; Colorectal Cancer
	Renal tubular acidosis	Acid-Base Disorders
	Post-hypocapnea	

Sign/Symptom	Differential Diagnosis	Section Title
Decreased anion gap	Renal failure Multiple myeloma Hypoalbuminemia Hypercalcemia Hypermagnesemia	Acute Renal Failure Multiple Myeloma and Other Plasma Cell Dyscrasias Calcium Homeostasis Hypermagnesemia
Metabolic alkalosis	Volume depletion, vomiting Hypokalemia Diuretics: loop and thiazide Chronic obstructive pulmonary disease Gittleman's syndrome Barter's syndrome Renal artery stenosis Juxtaglomerular cell tumor Conn's syndrome Little's syndrome Licorice ingestion	Hypokalemia Chronic Obstructive Pulmonary Disease Acute Renal Failure
Gastroenterology		
Upper gastrointestinal bleeding	Peptic ulcer disease Esophagitis Gastritis Esophageal varices Mallory-Weiss tear Arteriovenous malformations	Upper GI Bleeding Esophageal Disorders Esophageal Disorders; Upper GI Bleeding Upper GI Bleeding Upper GI Bleeding

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Sign/Symptom	Differential Diagnosis	Section Title
Gastroenterology (continued)		
Lower gastrointestinal bleeding	Dieulafoy's ulcer	Upper GI Bleeding
	Swallowed blood from oropharynx	
	Tumors and erosions	Upper GI Bleeding
	Infections	Upper GI Bleeding
	Medications	Upper GI Bleeding
	Diverticular disease	Lower GI Bleeding
	Arteriovenous malformations	Lower GI Bleeding
	Malignancy	Colorectal Cancer
	Rapid upper gastrointestinal bleed	Upper GI Bleeding
	Ischemic colitis	Lower GI Bleeding; Acute and Chronic Diarrhea
Ascites	Inflammatory bowel disease	Inflammatory Bowel Disease
	Infectious colitis	Lower GI Bleeding; Acute and Chronic Diarrhea
	Right heart failure	Complications following MI; Pulmonary Hypertension; Venous Thromboembolism; Congestive Heart Failure and Systolic Dysfunction
	Pericardial effusion ± tamponade	Pericarditis; Pericardial Effusions; Indications for Emergent Echocardiography
	Constrictive pericarditis	Diastolic Dysfunction, Restrictive Cardiomyopathy
	IVC occlusion/thrombosis	Ascites
	Veno-occlusive disease	Ascites

Sign/Symptom	Differential Diagnosis	Section Title
Jaundice	Budd-Chiari syndrome	Ascites
	Cirrhosis	Abnormal Liver Function Tests; Acute Viral Hepatitis; Acute Liver Failure; Ascites
	Portal vein thrombosis	Ascites
	Tuberculosis	Management of Tuberculosis
	Lymphoma	Hodgkin's Disease; Non-Hodgkin's Lymphoma
	Metastatic disease	Colorectal Cancer
	Primary mesothelioma	
	Systemic lupus erythematosus	Systemic Lupus Erythematosus
	Hypothyroidism	Thyroid Disease
	Renal failure	Acute Renal Failure
	Pancreatitis	Pancreatitis
	TIPS occlusion	Ascites
	Hemolysis	Evaluation of Anemia
	Ineffective erythropoiesis	
	Gilbert's syndrome	Abnormal Liver Function Tests
	Crigler-Najjar	Abnormal Liver Function Tests
	Cirrhosis	Abnormal Liver Function Tests; Acute Viral Hepatitis; Acute Liver Failure; Ascites
	Hepatitis	Acute Viral Hepatitis; Abnormal Liver Function Tests; Acute Liver Failure
	Dubin-Johnson syndrome	Abnormal Liver Function Tests
	Rotor syndrome	Abnormal Liver Function Tests

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Sign/Symptom	Differential Diagnosis	Section Title
Gastroenterology (continued)		
	Primary biliary cirrhosis	Biliary Disease
	Medication/drug toxicity	Toxidromes
	Primary sclerosis cholangitis	Biliary Disease
	Sepsis	Sepsis
	Pregnancy	
	Choledocholithiasis	Biliary Disease
	Pancreatic malignancy	
	Biliary malignancy	Biliary Disease
	Acute liver failure	Acute Liver Failure; Abnormal Liver Function Tests
Acute abdominal pain	Appendicitis	
	Diverticulitis	
	Pelvic inflammatory disease	Lower GI Bleeding
	Ovarian torsion	
	Tubo-ovarian abscess	
	Colitis	Lower GI Bleeding; Inflammatory Bowel Disease; Acute and Chronic Diarrhea
	Large bowel obstruction	
	Aortic dissection	Aortic Dissection; Hypertensive Crises
	Abdominal aortic aneurysm rupture	
	Small bowel obstruction	

Sign/Symptom	Differential Diagnosis	Section Title
Chronic diarrhea	Mesenteric ischemia	Lower GI Bleeding; Acute and Chronic Diarrhea
	Hepatitis	Acute Viral Hepatitis; Abnormal Liver Function Tests; Acute Liver Failure
	Cholecystitis	Biliary Disease
	Cholangitis	Biliary Disease
	Cholelithiasis	Biliary Disease
	Pancreatitis	Pancreatitis
	Peptic ulcer disease	Upper GI Bleeding
	Gastritis	
	Splenic infarction	
	Lower lobe pneumonia	Pneumonia; Nosocomial Pneumonia; Management of Tuberculosis
	Myocardial ischemia/infarction	Ischemic Heart Disease
	Diarrhea	Acute and Chronic Diarrhea
	Inflammatory bowel disease	Inflammatory Bowel Disease
	Malabsorption	Acute and Chronic Diarrhea
Hematology	Lactose intolerance	Acute and Chronic Diarrhea
	Secretory states	Acute and Chronic Diarrhea
	Infection	Acute and Chronic Diarrhea
	Hypermotility syndromes	
Polycythemia	Polycythemia vera	Myelodysplastic and Myeloproliferative Disorders
	Chronic hypoxemia	

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Sign/Symptom	Differential Diagnosis	Section Title
Hematology (<i>continued</i>)		
Thrombocytopenia	Carboxyhemoglobinemia	Abnormal Liver Function Tests
	Renal cell carcinoma	
	Hepatocellular carcinoma	
	Cerebellar hemangioblastomas	
	Hypertestosteronemia	
	Hypercortisolism	
	Postrenal transplantation	
	Aplastic anemia	Evaluation of Anemia
	Hematological malignancy	
	Myelodysplasia	
		ALL; AML; CLL; CML; Platelet Disorders
		Myelodysplastic and Myeloproliferative Disorders
	Megaloblastic anemia	Evaluation of Anemia
	Chronic alcoholism	
	Idiopathic thrombocytopenic purpura	Platelet Disorders
	Thrombotic thrombocytopenic purpura	Platelet Disorders
	Medication toxicity	
	Systemic lupus erythematosus	Systemic Lupus Erythematosus
	Sepsis	Sepsis
	Chronic lymphocytic leukemia	CLL
	Hypersplenism	
	Hemolytic uremic syndrome	Platelet Disorders

Sign/Symptom	Differential Diagnosis	Section Title
Thrombocytosis	Disseminated intravascular coagulation	Platelet Disorders; Sepsis; Tick-Borne Illnesses
	Viral infections	
	HIV	HIV and Its Complications; Acute Retroviral Syndrome
	Liver failure	Fulminant Hepatic Failure
	Essential thrombocytosis	
Neutropenia	Acute blood loss	Evaluation of Anemia; Upper GI Bleeding; Lower GI Bleeding; Evaluation of Hemoptysis
	Iron deficiency	Evaluation of Anemia
	Infection	Sepsis
	Inflammatory response	
	Postsplenectomy	
	Postalcohol suppression	
	Malignancy	
	Postchemotherapy	
	Overwhelming sepsis	Sepsis
	Cyclic neutropenia	
	Marrow infiltration	
	B ₁₂ deficiency	Evaluation of Anemia
	Folate deficiency	Evaluation of Anemia
	HIV infection	HIV and Its Complications; Acute Retroviral Syndrome
	Fungal infection	
	Typhoid	Organisms and Gram Stains; Abnormal Liver Function Tests
	Brucellosis	Organisms and Gram Stains
	Felty's syndrome	

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Sign/Symptom	Differential Diagnosis	Section Title
Hematology (continued)		
Neutrophilia	Hereditary neutrophilia	
	Myeloproliferative disorders	Myelodysplastic and Myeloproliferative Disorders
	Leukemoid reaction	
	Cigarette smoking	
	Acute infection	Sepsis
	Chronic inflammation	
	Myocardial infarction	Ischemic Heart Disease
	Excessive exercise	
	Corticosteroid use	Adrenal Insufficiency
	Lithium	Toxidromes
	Hemolytic anemias	Evaluation of Anemia
	Immune thrombocytopenic purpura	Platelet Disorders
	Sickle cell anemia	Evaluation of Anemia
	Marrow invasion	
	Solid tumors	Lung Cancer; Colorectal Cancer; Prostate Cancer; Breast Cancer
	Sweet's syndrome	
	Heat stroke	
	Asplenia	
Eosinophilia	Lymphoma	Hodgkin's Disease; Non-Hodgkin's Lymphoma
	Asthma	The Other Obstructive Lung Diseases

Sign/Symptom	Differential Diagnosis	Section Title
	Allergic bronchopulmonary aspergillosis	The Other Obstructive Lung Diseases; Pneumonia
	Drug reaction	
	Parasitic infections	Acute and Chronic Diarrhea
	Atopy	
	Churg-Strauss syndrome	Small Vessel Vasculitis
	Rheumatoid arthritis	Arthritis
	Systemic lupus erythematosus	Systemic Lupus Erythematosus
	Acute lymphoblastic leukemia	Acute Lymphoblastic Leukemia
	Sezary syndrome	Non-Hodgkin's Lymphoma
	Some solid tumors	Lung Cancer; Colorectal Cancer; Prostate Cancer; Breast Cancer
	Eosinophilic pneumonia	
	Loeffler's endocarditis	Infective Endocarditis
	Adrenal insufficiency	Adrenal Insufficiency
Basophilic stippling	Anemia	Evaluation of Anemia
	Heavy metal poisoning	
Target cells	Hemoglobin C disease	Evaluation of Anemia
	Liver disease	Abnormal Liver Function Tests; Acute Viral Hepatitis; Acute Liver Failure
	Thalassemia minor	Evaluation of Anemia
	Postsplenectomy	
Teardrop cells	Marrow infiltration	

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Sign/Symptom	Differential Diagnosis	Section Title
Hematology (<i>continued</i>)		
	Myelofibrosis	Myelodysplastic and Myeloproliferative Disorders
Helmet cells	Hemolysis Disseminated intravascular coagulation Microangiopathic hemolytic anemia	Evaluation of Anemia Platelet Disorders; Sepsis Evaluation of Anemia
Howell-Jolly bodies	Postsplenectomy Hemolysis Thalassemia Pernicious anemia	Evaluation of Anemia
Heinz bodies	G-6-PD deficiency Thalassemia	Evaluation of Anemia Evaluation of Anemia
Pappenheimer's bodies	Sideroblastic anemia Thalassemia	Evaluation of Anemia Evaluation of Anemia
Disseminated intravascular coagulopathy	Sepsis Eclampsia/HELLP syndrome Placental abruption Promyelocytic leukemia	Sepsis Platelet Disorders AML
Central Nervous System		
Altered mental status	Seizure Neoplasm	

Sign/Symptom	Differential Diagnosis	Section Title
	Intracerebral hemorrhage	Intracranial Hemorrhage
	Stroke	Stroke
	Hypoglycemia	
	Hyponatremia	Hyponatremia
	Hypernatremia	Hypernatremia
	Hypercalcemia	Calcium Homeostasis
	Hypermagnesemia	Hypermagnesemia
	Uremia	Acute Renal Failure
	Hyperammone-mia	Abnormal Liver Function Tests; Acute Viral Hepatitis
		Acute Liver Failure; Hepatic Encephalopathy
	Hypothyroidism	Thyroid Disease
	Adrenal insufficiency	Adrenal Insufficiency
	Low cardiac output	Congestive Heart Failure; Diastolic Dysfunction,
	Medication/drug toxicity	Toxidromes
	Alcohol withdrawal	Toxidromes
	Meningitis/encephalitis	Meningitis and Encephalitis
	Sepsis	Sepsis
	Hepatic encephalopathy	Hepatic Encephalopathy
	Acute liver failure	Acute Liver Failure
	Rocky Mountain spotted fever	Tick-Borne Illnesses

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COMMONLY USED FORMULAS

Cardiology

Cardiac Output (CO) = Stroke Volume (mL) $\times$ HR (bpm) / 1000 $\rightarrow$
in L/min

QTc (msec) = QT / $\sqrt{\text{RR}}$

Rate Pressure Product (RPP) = HR $\times$ SBP

Mean Arterial Pressure (MAP) = $2/3$ (DBP) + $1/3$ (SBP)

Pulse Pressure (PP) = SBP - DBP

Metabolic Equivalents (METS) = VO_2 / 3.5

Excellent: ≥ 13

Good: 10-12

Fair: 7-9

Reduced: 5-6

Poor: ≤ 4

Body Mass Index (BMI) = Weight (kg) / [Height (m)]²

Pulmonology

Alveolar-arterial (A-a) gradient = $150 - (\text{PaO}_2 + 1.25 \text{ PaCO}_2)$
(normal $\leq \text{age}/4 + 2.5$)

Oxygen transport to tissues (DO_2) = C.O. $\times$ ($1.34 \times \text{Hgb} \times \text{SaO}_2$)

Ideal Body Weight (IBW) $\rightarrow$ in kg

Male = $51.65 + (1.85 \times (\text{Height (inches)} - 60))$

Female = $48.67 + (1.65 \times (\text{Height (inches)} - 60))$

Static Compliance (during mechanical ventilation) = (Minute Tidal
Volume (mL)) / (Plateau Pressure (cm H₂O) - PEEP (cm H₂O))

normal = 70 - 100 mL/cm H₂O

Critical Care

Mean Pulmonary Artery Pressure (MPAP) = $[(2 \times \text{Diastolic PA Pressure}) + \text{Systolic PA Pressure}] / 3$

Fick CO:

CO = O₂ consumption / (Arterial-Venous O₂ Content) =

$\text{VO}_2 / (\text{CaO}_2 - \text{CvO}_2) = \text{VO}_2 (\text{mL/min}) / [13.4 \times \text{Hb (g/dL)} \times$
 $(\text{SaO}_2 - \text{SvO}_2)] \rightarrow$ in mL/min

SaO_2 = arterial oxygen saturation (%)

SvO_2 = venous oxygen saturation (%)

Cardiac Index (CI) = CO / Body Surface Area (BSA) $\rightarrow$ in L/min/m²

Systemic Vascular Resistance (SVR) = $80 \times [\text{MAP (mm Hg)} - \text{RA Pressure (mm Hg)}] / \text{CO (L/min)}$

Pulmonary Vascular Resistance (PVR) = $80 \times [\text{Mean PA Pressure (mm Hg)} - \text{Mean Capillary Wedge Pressure (mm Hg)}] / \text{CO (L/min)}$

Nephrology

Serum Anion Gap = $\text{Na (mEq/L)} - (\text{Cl (mEq/L)} + \text{HCO}_3 \text{ (mEq/L)})$

Delta Gap = Anion Gap - 12

Expected Respiratory Compensation for Metabolic Acidosis

$[(1.5 \times \text{Serum HCO}_3 \text{ (mEq/L)}) + 8] \pm 2 = \text{Expected PCO}_2$

Expected Respiratory Compensation for Metabolic Alkalosis

$15 + \text{Serum HCO}_3 \text{ (mEq/L)} = \text{Expected PCO}_2$

Fractional Excretion of Sodium (FENa) = $[(\text{Urine Na (mEq/L)} \times \text{Serum Cr (mg/dL)}) / (\text{Serum Na (mEq/L)} \times \text{Urine Cr (mg/dL)})] \times 100$

Osmolality = $2 [\text{Na}] + \text{BUN} / 2.8 + \text{glucose} / 18$

Osmolal Gap = Osm (measured) - Osm (calculated) (normal gap <20)

Urine Anion Gap = $\text{Urine Na (mEq/L)} + \text{Urine K (mEq/L)} + \text{Urine Cl (mEq/L)}$

Creatinine Clearance (from timed urine sample) = $[\text{Urine Cr (mg/dL)} \times \text{Urine Volume (mL)}] / [\text{Serum Cr (mg/dL)} \times \text{Collection Time (minutes)}]$

normal (male) - 90-130 mL/min; normal (female) - 80-125 mL/min

Creatinine Clearance (Cockcroft-Gault) =

For male: $[(140 - \text{Age (years)}) \times \text{Body Weight (kg)}] / [72 \times \text{Serum Cr (mg/dL)}]$

For female: $[(140 - \text{Age (years)}) \times \text{Body Weight (kg)}] / [85 \times \text{Serum Cr (mg/dL)}]$

Total Body Water (TBW) = $\text{Body Weight (kg)} \times \text{R-value}$

Children: 0.6

Males <65: 0.6

Females <65: 0.5

Males >65: 0.5

Females >65: 0.45

Correction of Hyponatremia

$$\text{Change in Serum Na (mEq/L)} = [\text{Infusate Na Concentration (mEq/L)} - \text{Serum Na (mEq/L)}] / (\text{TBW (L)} + 1)$$

Gastroenterology

$$\text{Stool Osmotic Gap} = [290 \text{ mOsm/kg} - 2 \times ([\text{Na}] + [\text{K}])]$$

$$\text{Serum-Ascites Albumin Gradient (SAAG)} = \text{Serum Albumin} - \text{Ascitic Fluid Albumin}$$

High gradient >1.1

Low gradient <1.1

Endocrinology

$$\text{Corrected Calcium} = \text{Serum Calcium} + [(4 - \text{Serum albumin}) \times 0.8]$$

$$\text{Corrected Na for Hyperglycemia} = \text{Measured Sodium} + [(\text{Serum Glucose} - 100) / 100] \times 1.6, \text{ or}$$

$$\text{Corrected Na for Hyperglycemia} = \text{Measured Sodium} + 0.016 \times (\text{Serum Glucose} - 100)$$

Infectious Disease

$$\text{Absolute Neutrophil Count (ANC)} = \text{WBC} \times (\% \text{ Neutrophils} + \% \text{ Bands})$$

Hematology-Oncology

$$\text{Reticulocyte Index (corrected for anemia)} = [\text{Observed Retic Count} (\%) \times (\text{Hct} / 45)] / 1\%$$

$$\text{Reticulocyte Production Index} = \text{Reticulocyte Index} / \text{Maturation Time (days)}$$

Maturation Time:	Hct	Days
	40–45%	1.0
	35–39%	1.5
	25–34%	2.0
	15–24%	2.5
	5–14%	3.0

RPI <2 – Ineffective Erythropoiesis

RPI 2–3 – Borderline Response

RPI > 3 – Adequate Response

Miscellaneous

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT FOR ALCOHOL (CIWA-AR) SCALE

Presenting Symptom	Range of Score
Nausea and Vomiting	0 = No nausea or vomiting 4 = Intermittent nausea with dry heaves 7 = Constant nausea and frequent vomiting
Paroxysmal Sweats	0 = No sweat visible 4 = Beads of sweat noted 7 = Drenching sweats
Agitation	0 = Normal activity 4 = Moderately fidgety and restless 7 = Constantly thrashes about
Anxiety	0 = No anxiety and at ease 4 = Moderately anxious or guarded 7 = Panic attacks
Auditory Disturbances	0 = Not present 4 = Moderately severe hallucinations 7 = Constant hallucinations
Visual Disturbances	0 = Not present 4 = Moderately severe hallucinations 7 = Constant hallucinations
Tactile Disturbances	0 = Not present 4 = Moderately severe hallucinations 7 = Constant hallucinations
Clouding of Sensorium	0 = Oriented and can do serial additions 1 = Cannot do serial additions 4 = Disoriented to place and/or person
Headache	0 = Not present 4 = Moderately severe 7 = Extremely severe
Tremor	0 = No tremor 4 = Moderate, with arms extended 7 = Severe, even without arms extended

A

- Abdominal pain, acute,
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- Abscess
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- Acute aortic insufficiency, 130t
- Acute chest pain, 857t
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