AudioDigest

INTERNAL MEDICINE
Board Review
2nd EDITION

Written Summaries

Wolters Kluwer

Lecture IMBR190101

Hypertension

Joseph Izzo, MD

The goal of this program is to improve the knowledge of physicians of the pathophysiology of hypertension and to present recommendations from recent guidelines regarding classification and treatment. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain the pathophysiology of hypertension and how hypertension varies between individuals and within individuals.*
2. *Recognize and distinguish between classifications of hypertension presented by several recent guidelines.*
3. *Explain and implement the recommended approaches to BP measurement and hypertension management, including recommended approaches to pharmacotherapy.*

Lecture IMBR190102

Complicated Hypertension and Special Situations in Hypertension Management

Joseph Izzo, MD

The goal of this program is to improve the awareness of current practice for diagnosis and management of resistant hypertension and hypertensive emergencies. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the definition of resistant hypertension.*
2. *Recognize that the prevalence of secondary hypertension is increased in resistant hypertension.*
3. *Discuss considerations for identification and treatment of hypertensive urgencies versus emergencies.*
4. *Identify and implement the different management approaches for hypertensive urgencies and emergencies.*

Lecture IMBR190103

Dyslipidemia and Large Artery Disease

Parag Joshi, MD, MHS

The primary goal of this program is to improve the knowledge of physicians of dyslipidemia related to atherosclerotic cardiovascular disease, including recommendations for monitoring and management, as well as knowledge regarding the large artery diseases. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain how cholesterol and triglycerides are metabolized and relate this to both atherosclerotic cardiovascular disease and lipid-lowering therapies.*
2. *Identify the most effective ways to manage dyslipidemia based on recent guidelines, including lifestyle and pharmacologic interventions.*
3. *Describe the risk factors, recommended screening approaches, and management of thoracic aortic diseases, abdominal aortic aneurysm, and peripheral artery disease.*

Lecture IMBR190104

Coronary Artery Disease

Deepak Bhatt, MD, MPH

The goal of this program is to improve the diagnosis and management of the spectrum of coronary artery disease (CAD). Upon completion of this program, the internist will be better able to:

1. *Describe the different manifestations of CAD.*
2. *Explain different diagnostic tests for evaluating CAD and their appropriate usage.*
3. *Identify treatment modalities for CAD, including revascularization and medical therapies.*
4. *Recognize when to use or avoid stress testing.*

Lecture IMBR190105

Heart Failure

Ileana Piña, MD, MPH

The goal of this program is to improve the diagnosis and management of heart failure in the adult patient. Upon completion of this program, the clinician will be better able to:

1. *Describe the general pathogenesis of heart failure.*
2. *Identify the various causes of heart failure.*
3. *Differentiate the forms of heart failure (ie, HFrEF, HFpEF).*
4. *Recognize the different types of medications for heart failure and their appropriate usage.*

Lecture IMBR190106

Valvular and Structural Heart Diseases

Deepak Bhatt, MD, MPH

The goal of this program is to improve the diagnosis and management of valvular and structural heart diseases. After hearing and assimilating this program, the clinician will be better able to:

1. *Select appropriate treatment of aortic stenosis and other valvular heart diseases.*
2. *Identify advantages and disadvantages of mechanical and bioprosthetic heart valves that contribute to selection for use.*
3. *Define the surgical and percutaneous options for mitral regurgitation.*
4. *Describe the emergent nature of pericardial tamponade and describe the appropriate treatments.*

Lecture IMBR190107

Cardiac Arrhythmias

Jeffery Anderson, MD

The goal of this program is to improve understanding of the etiology and treatment of cardiac arrhythmias. After reading, the clinician will be better able to:

1. *Describe the heart's electrical conduction system.*
2. *Identify major types of supraventricular arrhythmias.*
3. *Discuss the prevention of sudden cardiac death in patients with ventricular arrhythmias.*
4. *Discuss the treatment of heart block in patients with bradycardias and conduction system disorders.*

Lecture IMBR190108

Pulmonary Diseases

Daniel Ouellette, MD

The goal of this program is to improve awareness of the appropriate diagnostic tests and evaluation of a patient with lung disease, evidence-based asthma treatment, and interventions for reducing exacerbations of chronic obstructive pulmonary disease. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the appropriate use of the pulmonary diagnostic laboratory.*
2. *Identify common pulmonary diseases through appropriate patient evaluation.*
3. *Discuss evidence-based treatments for asthma.*
4. *Identify interventions that will reduce exacerbations of chronic obstructive pulmonary disease.*

Lecture IMBR190109

Pulmonary Disease: Bronchiectasis and Cystic Fibrosis, Diffuse Parenchymal Lung Disease, Occupational and Environmental Lung Disease, Pleural Disease, and Pulmonary Vascular Disease

Laura E. Crowley, MD

The goal of this program is to improve the awareness of current practice for diagnosis and management of bronchiectasis and cystic fibrosis, diffuse parenchymal lung disease, occupational and environmental disease, pleural disease, and pulmonary vascular disease. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain appropriate diagnosis and management of bronchiectasis and cystic fibrosis.*
2. *Identify the 5 main categories of diffuse parenchymal lung disease.*
3. *Discuss the key elements of exposure history and conditions that should increase clinical suspicion of an occupational lung disease.*
4. *Describe the 2 main types of abnormalities that affect the pleura, including clinical diagnostic criteria.*
5. *List the 5 groups of pulmonary hypertension and pulmonary arterial hypertension.*

Lecture IMBR190110

Lung Cancer

Dharani K. Narendra, MBBS

The goal of this program is to improve the comprehension of managing solitary pulmonary nodules, lung cancer, and mediastinal masses. Upon completion of this program, the clinician will be better able to:

1. *Evaluate and understand pulmonary nodules.*
2. *Explain the different types of lung cancer and rare tumors.*
3. *Discuss treatment options for different types of lung cancer.*
4. *Understand mediastinal anatomy and different tumors associated with each region.*

Lecture IMBR190111

Critical Care Medicine

Jose Pascual, MD, PhD
Ryan Dumas, MD

The goal of this program is to improve the awareness of the importance of identification of a critically ill patient, assessment of volume status, and key approaches for care regarding the neurological and respiratory systems. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the need for and types of mechanical ventilation.*
2. *Identify the types of shock and appropriate methods for volume resuscitation.*
3. *Discuss the importance of identifying delirium.*
4. *Identify appropriate treatments for acute respiratory distress syndrome.*

Lecture IMBR190112

Common Sleep Disorders

Shirin Shafazand, MD

The goal of this program is to improve the awareness of common sleep disorders encountered in internal medicine practice. After participating in this program, the physician will be better able to:

1. *Identify the signs and symptoms of sleep disordered breathing.*
2. *Identify the components of a focused history and physical examination for patients presenting with complaints of insomnia.*
3. *Discuss restless leg syndrome as a possible differential diagnosis in patients who report insomnia.*

Lecture IMBR190113

Altitude Illness

Benjamin Honigman, MD

The goal of this program is to improve the comprehension of altitude illness in the adult patient, including common types of altitude illness and air travel requirements for patients with pulmonary disease. Upon completion of this program, the clinician will be better able to:

1. *Describe the general pathogenesis of altitude illness.*
2. *Discuss acute mountain sickness, high altitude pulmonary edema, and high altitude cerebral edema.*
3. *Explain requirements for air travel in patients with underlying respiratory disease.*

Lecture IMBR190114

Acute Kidney Injury

Pedram Fatehi, MD, MPH

The goal of this program is to improve the awareness of current practice for evaluation and etiologies of acute kidney injury. After hearing and assimilating this program, the clinician will be better able to:

1. *Identify the terminology used to describe acute kidney injury.*
2. *Discuss the most appropriate laboratory tests to evaluate the various forms of acute kidney injury.*
3. *Explain postrenal, prerenal, intrinsic, and multimechanism etiologies of acute kidney injury.*

Lecture IMBR190115

Chronic Kidney Disease and Tubulointerstitial Diseases

Mitchell H. Rosner, MD

The goal of this program is to improve the diagnosis and management of chronic kidney disease and acute and chronic tubulointerstitial disease. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss appropriate staging and referral of patients with chronic kidney disease.*
2. *Identify common complications of chronic kidney disease, including cardiovascular disease, anemia, metabolic acidosis, and bone mineral metabolism disorders.*
3. *Explain characteristic clinical manifestations of tubulointerstitial disease.*
4. *Identify etiologies that can lead to chronic tubulointerstitial nephritis, including autoimmune, toxic, hereditary, infection-related, and medication-related causes.*

Lecture IMBR190116

Diagnosis and Management of Glomerulonephritis

Mitchell H. Rosner, MD

The goal of this program is to improve the comprehension of the pathophysiology of different forms of glomerular disease, as well as to better understand their treatments and prognoses. Upon completion of this program, the clinician will be better able to:

1. *Understand the pathophysiology of nephrotic syndromes and nephritic syndromes.*
2. *Discuss and compare common diseases associated with nephrotic and nephritic syndromes.*
3. *Diagnose common diseases associated with glomerular dysfunction.*
4. *Evaluate and determine treatment of and prognosis for common diseases associated with glomerular dysfunction.*

Lecture IMBR190117

Nephrology

Joel Topf, MD

The goal of this program is to improve the understanding the clinical presentation, diagnosis, and treatment of the most common conditions seen by a nephrologist. Upon completion of this program, the clinician will be better able to:

1. *Explain the diagnosis and treatment of urinary tract infections.*
2. *istinguish the types of kidney problems in pregnant women.*
3. *Recognize and evaluate polycystic kidney disease.*
4. *Differentiate the different types of kidney stones and their appropriate treatment.*

Lecture IMBR190118

Fluid, Electrolyte, and Acid-base Disorders

Pedram Fatehi, MD

The goal of this program is to improve the understanding of the physiology underlying fluid, electrolyte, and acid-base disorders, the conditions or diseases associated with those disorders, as well as their clinical evaluation and management and strategies for the diagnosis of patients with those disorders. After hearing and assimilating this program, the clinician will be better able to:

1. *Review the physiology underlying fluid, electrolyte, and acid-base disorders.*
2. *List the conditions or diseases associated with the various fluid, electrolyte, and acid-base imbalances, and explain strategies for clinical evaluation and management.*
3. *Discuss case studies of patients with fluid, electrolyte, or acid-base disorders and delineate strategies for the diagnosis of patients with those disorders.*

Lecture IMBR190119

Stroke and Cognitive Impairment

Vasileios-Arsenios Lioutas, MD

The goal of this program is to improve the awareness of current practice for diagnosis and management of ischemic and hemorrhagic stroke and intracranial aneurysms and subarachnoid hemorrhage. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain similarities and differences between ischemic and hemorrhagic stroke in terms of imaging methods, laboratory tests, and blood pressure management.*
2. *Identify the major subtypes of ischemic stroke.*
3. *Relate considerations for secondary prevention of stroke and TIA.*
4. *Categorize screening and monitoring recommendations for intracranial aneurysm and subarachnoid hemorrhage.*

Lecture IMBR190120

Obesity and Metabolic Syndrome

Caroline Apovian, MD

The goal of this program is to improve the diagnosis and management of overweight, obesity, and metabolic syndrome, especially knowledge and application of lifestyle interventions as well as pharmacologic and surgical treatment. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain how to assess and diagnose overweight, obesity, and metabolic syndrome.*
2. *Effectively develop and communicate a plan for lifestyle interventions, including diet and exercise, with appropriate follow-up.*
3. *Identify indications for the use of pharmacologic and surgical therapies, including benefits and risks of different approaches as well as data on outcomes.*

Lecture IMBR190121

Pituitary, Adrenal, and Thyroid Disease

John Carmichael, MD

The goal of this program is to improve the awareness of pituitary, thyroid, and adrenal disorders and their evaluation and management. After hearing and assimilating this program, the clinician will be better able to:

1. *Identify the clinical signs and symptoms of hypo- and hyperpituitarism.*
2. *Discuss the evaluation and management of hyper- and hypothyroidism.*
3. *Explain the evaluation and treatment of common adrenal disorders.*

Lecture IMBR190122

Calcium and Bone Metabolism

Mike Lewiecki, MD

The primary goal of this program is to improve physicians' knowledge of calcium and bone physiology and pathophysiology, including understanding the role of diet and absorption, recommendations for monitoring, screening, and management of conditions such as osteoporosis. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain how calcium and vitamin D are obtained through the diet as well as causes of deficiencies and malabsorption:*
2. *Evaluate and treat hypercalcemia, hypocalcemia, and vitamin D deficiency.*
3. *Explain and use the most effective approaches to screening and management of osteoporosis, including the detailed recommendations for initiation of and holidays from pharmacologic therapy.*

Lecture IMBR190123

Reproductive Health

Bradley Hurst, MD

The goal of this lecture is to understand amenorrhea, infertility, and menopause. Upon completion of this program, the clinician will be better able to:

1. *Evaluate and treat women with amenorrhea.*
2. *Diagnose polycystic ovarian syndrome.*
3. *Determine the cause of infertility.*
4. *Treat women with vasomotor symptoms due to menopause.*

Lecture IMBR190124

Recurrent Urinary Tract Infections and Female Incontinence and Urgency

Erinn Myers, MD

The goal of this lecture is to improve understanding of evaluation and treatment of women with urinary tract infections, urinary incontinence, and urgency. Upon completion of this program, the clinician will be better able to:

1. *Identify the risk factors for urinary tract infection.*
2. *Evaluate a patient with urinary incontinence or urgency.*
3. *Treat a patient with urinary incontinence, urgency, or urinary tract infection.*

Lecture IMBR190125

Testosterone Deficiency and Replacement

Joseph Alukal, MD

The goal of this program is to improve the understanding of testosterone replacement and associated risks and benefits. After reading, the clinician will be able to:

1. *Describe the diagnosis of male hypogonadism.*
2. *Identify the methods of testosterone replacement.*
3. *Describe the health benefits and risks of testosterone replacement.*
4. *Discuss data on the cardiac safety of testosterone replacement.*

Lecture IMBR190126

The General Approach to the Treatment and Prevention of Infections

Marisa Holubar, MD

The goal of this program is to improve the awareness of current practice for management of patients with infections, use of common antimicrobials, and adult vaccinations. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the importance of antimicrobial stewardship, including the choice, dosing, route, and duration of antibiotic administration.*
2. *Identify commonly used new and "old" antibiotics.*
3. *Discuss recommendations for adult vaccinations, including the influenza, pneumococcal, varicella zoster, and hepatitis B vaccines.*

Lecture IMBR190127

Lung Infections

Vickie R. Shannon, MD

The goal of this program is to improve the understanding of the clinical presentation, diagnosis, and treatment of pneumonia. Upon completion of this program, the clinician will be better able to:

1. *Determine appropriate diagnostic procedures for patients presenting with pneumonia.*
2. *Recognize the characteristics of different types of pneumonia.*
3. *Identify potential causative agents of pneumonia based on presentation and history.*
4. *Discuss different types of tuberculosis.*

Lecture IMBR190128

Tuberculosis and Pneumonia

Vickie R. Shannon, MD

The goal of this program is to improve the physician's knowledge of pulmonary diseases, including fungal pneumonias and related mycoses; bacterial infections, including those caused by mycoplasmas; and diseases associated with HIV infection. After hearing and assimilating this program, the clinician will be better able to:

1. *Identify the different types of fungal pulmonary infections and pneumonias and their diagnosis and management.*
2. *Distinguish bacterial pulmonary infections, especially tuberculosis and nontuberculosis mycoplasma infections, including differences in their diagnosis and management.*
3. *Explain the effects of HIV coinfection and immune function on the development and management of pulmonary disease.*

Lecture IMBR190129

HIV/AIDS Update

Roy Gulick, MD

The goal of this program is to provide updates on the epidemiology, clinical course, treatment, and prognosis of HIV infection. Upon completion of this program, the clinician will be better able to:

1. *Discuss the current epidemiology of HIV and AIDS and compare it with previous trends.*
2. *Explain the clinical course and pathophysiology of HIV infection and AIDS.*
3. *Identify the treatment options available for HIV infection.*
4. *Understand the prognosis for patients with HIV and AIDS, both treated and untreated.*

Lecture IMBR190130

Health Advice for Travelers; Ticks and Tick-borne Infections

Ken Dardick, MD

The goal of this program is to improve the awareness of current practice for providing current information to travelers and the risks, diagnosis, and management of tick-borne infection. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the epidemiology and basic science of travel medicine.*
2. *Identify destination-specific risks to travelers.*
3. *Discuss tick biology, including identification of relevant pathogens.*
4. *Discuss appropriate interpretation of diagnostic tests and treatment of tick-borne infections.*

Lecture IMBR190131

Skin and Soft Tissue Infections; Osteomyelitis; CNS Infections

John K. Crane, MD, PhD

The goal of this program is to improve the awareness of current practice for diagnosis and management of skin and soft tissue infections, osteomyelitis, and CNS infections. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss and use appropriate imaging methods and antibiotic management of cellulitis, boils, and surgical site infections;*
2. *Identify contraindications for nuclear medicine scans in the evaluation of osteomyelitis;*
3. *Discuss and implement microbial diagnosis and treatment in osteomyelitis;*
4. *Identify CNS infections on the rise in the US.*

Lecture IMBR190132

Healthcare-associated Infections and the US Healthcare System

Marisa Holubar, MD

The goal of this program is to provide an overview of healthcare-associated infections (HAIs) and their impact on the US healthcare system, as well as their diagnosis, management and prevention. Upon completion of this program, the clinician will be better able to:

1. *List the common healthcare-associated infections (HAIs) and describe their diagnosis and prevention.*
2. *Explain the importance of appropriate hand hygiene.*
3. *Describe the various laboratory methods used to diagnose C. diff.*
4. *Discuss the difference between organism colonization and cause of infection in laboratory tests relating to common healthcare-associated infections.*
5. *Recommend appropriate antibiotics to treat common HAIs, including C. diff, CAUTIs, VAP, and CLABSIs.*

Lecture IMBR190133

Hemostasis and Thrombosis

Evan Martin Bloch, MBChB, MD, MS

The goal of this program is to improve the awareness of major bleeding and clotting disorders and underlying mechanisms, tests or assays for bleeding and clotting disorders and how to interpret them, and transfusion management with focus on blood types, transfusion triggers, and transfusion reactions. After hearing and assimilating this program, the clinician will be better able to:

1. *Review major bleeding and clotting disorders and underlying mechanisms.*
2. *Describe tests or assays for bleeding and clotting disorders and how to interpret them.*
3. *Discuss transfusion management with focus on blood types, transfusion triggers, and transfusion reactions.*

Lecture IMBR190134

Dementia, Delirium and Assessment of Decision-making Capacity

Yesne Alici, MD

The goal of this program is to improve the awareness of current practice for the diagnosis and management of dementia and delirium and to educate regarding decision-making capacity in healthcare settings. After hearing and assimilating this program, the clinician will be better able to:

1. *Identify the clinical presentations for various forms of dementia and how they differ from delirium.*
2. *Discuss possible underlying contributing factors to delirium.*
3. *Discuss the management of patients with delirium in the hospital setting.*
4. *Describe the assessment of a patient for health-related decision-making capacity.*

Lecture IMBR190135

Personality Disorders in the Medical Setting

Donald Black, MD

The goal of this program is to improve physicians' knowledge of personality disorders, including definitions and diagnostic criteria , recognition and assessment , and management . After hearing and assimilating this program, the clinician will be better able to:

1. *Distinguish between the 3 clusters and 10 different types of personality disorders, including major characteristics of the best-validated disorders.*
2. *Explain how internists and other physicians can recognize personality disorders, including important questions to ask and other approaches to distinguish those with personality disorders from others with similar traits.*
3. *Discuss the best ways to manage personality disorders, including approaches for working with difficult patients and suggested treatments.*

Lecture IMBR190136

Mood, Anxiety, and Psychotic Disorders in the Medical Setting

Donald Black, MD

The goal of this program is to improve the knowledge of physicians of the characteristics , diagnosis , and management of mood, anxiety, and psychotic disorders. After hearing and assimilating this program, the clinician will be better able to:

1. *Distinguish between the major characteristics of important mood, anxiety, and psychotic disorders that are commonly encountered in medical settings.*
2. *Identify the symptoms of common disorders and explain how they can be recognized in a medical setting.*
3. *Discuss appropriate management of mood, anxiety, and psychotic disorders with an emphasis on the role of the internist.*

Lecture IMBR190137

Addiction Medicine: Core Knowledge and Skills for Medical Clinicians

Jim Finch, MD

The primary goal of this program is to improve the knowledge of physicians of the presentation and management of substance use disorders, including understanding the best ways to detect these disorders in clinical practice, knowing the characteristics and management of the most commonly abused drugs, and being familiar with the most effective forms of intervention and treatment. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain and implement best ways of screening for substance use disorders;*
2. *Describe the characteristics of the most commonly abused drugs, including effects of their use;*
3. *Explain and implement the most effective approaches to intervention and treatment of patients with substance use disorders, including approaches that can be used in the clinic and indications that patients need more intensive treatment.*

Lecture IMBR190138

Hepatobiliary System

James Walter, MD

The goal of this program is to improve understanding of the hepatobiliary system and current practices regarding the diagnosis and management of liver and biliary diseases. Upon completion of this program, the clinician will be better able to:

1. *Describe the different manifestations of diseases of the hepatobiliary system, including complications of chronic liver disease.*
2. *Explain different diagnostic tests for evaluating diseases of the liver or biliary system.*
3. *Identify treatment modalities, including medical or surgical therapies.*

Lecture IMBR190139

Disorders of the Esophagus, Stomach, and Duodenum

Christopher Marshall, MD

The primary goal of this program is for the listener to understand the clinical presentation, diagnosis, and treatment of disorders of the esophagus, stomach, and duodenum. After hearing and assimilating this program, the clinician will be better able to:

1. *Select and implement appropriate diagnostic procedures and treatment options for patients with dysphagia, including solid food dysplasia (such as eosinophilic esophagitis) and other conditions of dysphagia, such as pill esophagitis, candida infection, viral disease, esophageal cancer, and motility disorders, such as achalasia.*
2. *Select and implement appropriate diagnostic procedures and treatment options for patients with GERD, including H. pylori infection and Barrett's esophagus.*
3. *Select and implement appropriate diagnostic procedures and treatment options for patients with dyspepsia, peptic ulcer disease, gastric cancer, gastric polyps, subepithelial lesions of the stomach, gastroparesis, gastric bypass surgery, and gastrointestinal bleeding.*

Lecture IMBR190140

Common Gastrointestinal Disorders Seen in Outpatient and Inpatient Settings

Christopher Marshall, MD

The goal of this program is to improve the understanding and management of common gastrointestinal diseases seen in hospital and outpatient settings. Upon completion of this program, the clinician will be better able to:

1. *Describe and recognize typical presentations of acute pancreatitis and other common gastrointestinal disorders.*
2. *Discuss and select diagnostic options for common gastrointestinal disorders.*
3. *Explain and use different management strategies and treatment modalities for common gastrointestinal disorders.*
4. *Identify patients that might benefit from referral to gastroenterologists for further diagnosis and treatment.*

Lecture IMBR190141

Approach to the Patient with a Suspected Rheumatologic Disease

Don Goldenberg, MD

The goal of this program is to improve the diagnosis of rheumatologic disease in the adult patient. Upon completion of this program, the clinician will be better able to:

1. *Describe and implement the steps in the approach to rheumatologic disease;*
2. *Discuss and perform differential diagnosis for suspected rheumatologic disease;*
3. *Use laboratory testing (eg, ESR, CRP)appropriately and effectively.*

Lecture IMBR190142

Arthritis Review

Diane M. Horowitz, MD

The goal of this program is to increase the knowledge and understanding of the diagnosis and management of osteoarthritis, other commonly encountered types of arthritis, and prosthetic joint infections. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the incidence, pathophysiology, diagnostic techniques, and management of osteoarthritis.*
2. *Identify the subtypes of osteoarthritis.*
3. *Characterize other types of arthritis encountered by clinicians.*
4. *Describe the incidence, diagnostic considerations, and management of patients with prosthetic joint infections.*

Lecture IMBR190143

Rheumatoid Arthritis and Systemic Lupus Erythematosus

Alexandra Villa-Forte, MD

The goal of this program is to gain an understanding of the clinical manifestation, diagnosis, and treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). After hearing and assimilating this program, the clinician will be better able to:

1. *List the common signs and symptoms of RA and SLE.*
2. *Outline the process of diagnosing a patient with suspected RA or SLE.*
3. *Discuss the challenges surrounding SLE diagnosis.*
4. *Summarize the treatment options for RA and SLE.*
5. *Discuss the importance of early diagnosis and early institution of disease-modifying treatment for patients with RA.*
6. *Explain the importance of treating atherosclerosis complications such as hypertension, hyperlipidemia, and diabetes in patients with RA and SLE.*

Lecture IMBR190144

Vasculitis, Systemic Sclerosis, Inflammatory Myopathies, and Fibromyalgia

Bruce Rothschild, MD

The goal of this program is to improve the comprehension of the systemic vasculitides, inflammatory myopathies, connective tissue disorders, and fibromyalgia in the adult patient. Upon completion of this program, the clinician will be better able to:

1. *Describe types of vasculitis, including types of vessels involved and patient presentation.*
2. *Analyze differential diagnoses for small-, medium-, and large-vessel vasculitis.*
3. *Explain methods for diagnosing and managing fibromyalgia.*
4. *Categorize types and treatments of inflammatory myopathies.*
5. *Differentiate types and treatments of connective tissue disorders.*

Lecture IMBR190145

Interpretation of the Medical Literature

Thomas Payne, MD

The goal of this program is to improve interpretation of the literature through concepts of incidence, prevalence, and risk; study design, and communication with patients. After hearing and assimilating this program, the clinician will be better able to:

1. *Discuss the relationships between test characteristics and positive/negative predictive value using a 2x2 table.*
2. *Identify the differences between observational and experimental study designs.*
3. *Discuss the concepts of statistical significance and clinical importance.*
4. *Identify the use of relative and absolute risk for discussions of risk with patients.*

Lecture IMBR190146

High Value Care, Patient Safety, and Quality Improvement

Lianne Marks, MD, PhD

The goal of this program is to improve the knowledge of physicians of current efforts and approaches to provide high value care while improving patient safety, and approaches to quality improvement. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain the difference between pay for reporting and pay for performance, including ways that these approaches may affect patient care and outcomes in specific situations.*
2. *Distinguish approaches to improve patient safety and reduce medical errors, with an understanding of how to implement these approaches.*
3. *Explain current quality improvement initiatives, including reporting requirements for physicians.*

Lecture IMBR190147

Routine Care of the Healthy Patient

Kevin Sherin, MD

The goal of this program is to improve the awareness of current practice for routine care of the healthy patient, including periodic health exams and screening recommendations. After hearing and assimilating this program, the clinician will be better able to:

1. *Better build trust with patients, understanding its importance in the provision of care to patients;*
2. *Identify and follow universal vaccine contraindications;*
3. *Understand and use appropriate considerations for genetic screening;*
4. *Understand the High Value Care statements and use them in the selection of screening tests.*

Lecture IMBR190148

Medical Care of the Pregnant Patient

Priscilla Pemu, MBBS, MSCR

The goal of this program is to improve the awareness of current practice for diagnosis and management of common medical conditions in the pregnant woman, including asthma, liver disease, and depression. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain the acute and chronic management of asthma during pregnancy.*
2. *Discuss the evaluation of liver disease in pregnancy.*
3. *Identify the considerations for management of depression in pregnancy.*

Lecture IMBR190149

Preoperative Medical Evaluation

Steven Cohn, MD

The goal of this program is to improve physicians' knowledge about preoperative evaluation, including recommendations for appropriate preoperative testing and medication management, ways to assess and manage cardiac and pulmonary risk, and recommendations for other specific conditions. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain what preoperative testing is appropriate and what testing is unnecessary for patients with specific risk factors and conditions, as well as general recommendations for medical management.*
2. *Recognize factors associated with increased cardiac and pulmonary risk and appropriate management.*
3. *Identify the best approaches to preoperative evaluation and management of patients with pulmonary, hematologic, endocrine, liver, and renal complications and conditions.*

Lecture IMBR190150

Pain Management

Timothy Deer, MD

The goal of this program is to improve the knowledge of physicians regarding types of pain and appropriate management for each and regarding the opioid crisis, including recommendations for reducing risks associated with pain management. After hearing and assimilating this program, the clinician will be better able to:

1. *Explain the different types of pain that are commonly encountered in the United States.*
2. *Describe and use appropriate management approaches for common types of pain, including newly approved therapies and those under development.*
3. *Explain and implement ways that clinicians can effectively manage pain while reducing associated risks and helping to address the opioid crisis.*

Lecture IMBR190151

Palliative Care

David Casarett, MD

The primary goal of this program is to improve the knowledge of physicians regarding palliative care, focusing on ways to improve communication and manage symptoms, including understanding the most effective ways to conduct difficult conversations, and including recommendations for treatment and management, especially with respect to pain medication choice and dyspnea. After hearing and assimilating this program, the clinician will be better able to:

1. *Conduct difficult conversations as effectively as possible and handle decision-making when a patient does not wish to have these conversations*
2. *Describe and use the recommended approaches for management and pain medication selection in palliative care*
3. *Explain and implement the most effective approaches to managing dyspnea in palliative care.*

Lecture IMBR190152

Geriatrics

Arthur D. Hayward, MD, MBA

The objective of this program is to improve awareness of the unique clinical challenges of geriatric patients and to understand the best approach to managing geriatric patients. After implementing the program, the clinician will be better able to:

1. *Identify the key components of a geriatric assessment.*
2. *Discuss falls and fall prevention in elderly patients.*
3. *Explain the process of deprescribing by the geriatrician.*
4. *Identify the different sources and treatment of urinary incontinence in elderly patients.*
5. *Describe the 5 stages and the best preventive methods of treating pressure ulcers.*

Lecture IMBR190153

Eye Diseases for the Internist

Anat Galor, MD, MSPH

The goal of this program is to improve the awareness of current practice for the evaluation of red eye and dry eye by internists. After hearing and assimilating this program, the clinician will be better able to:

1. *Identify common causes of red eye that may be seen in the clinic setting.*
2. *Distinguish between non-emergent and emergent causes of red eye and when to refer for ophthalmologic evaluation.*
3. *Distinguish between true dry eye and other eye conditions presenting with a dry eye sensation.*

Lecture IMBR190154

Allergic and Immunologic Disorders

Julie Wang, MD

The goal of this program is to improve the comprehension of allergic and immunologic disorders in the adult patient. Upon completion of this program, the clinician will be better able to:

1. *Evaluate the signs and symptoms of common allergic and immunologic disorders.*
2. *Understand the diagnostic approach and management strategies for these disorders.*
3. *Identify patients who would benefit from referral for further evaluation.*

Lecture IMBR190155

Psoriasis

Daniel Federman, MD

The goal of this program is to improve the comprehension of diagnosing and managing common dermatologic disorders in the adult patient. Upon completion of this program, the clinician will be better able to:

1. *Describe typical presentations for common dermatologic disorders.*
2. *Discuss differential diagnoses for common dermatologic disorders.*
3. *Explain different management strategies and treatment modalities for common dermatologic disorders.*
4. *Identify patients that might benefit from referral to dermatologists for further diagnosis and treatment.*

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Hypertension

Joseph Izzo, MD, *Professor of Medicine and Pharmacology, State University of New York at Buffalo, Buffalo, New York*

Overview: important to understand basic pathophysiology as well as clinical trials and guidelines; can apply information about physiology and pathophysiology directly to patient care; hypertension not a disease; blood pressure (BP) is continuously distributed in population; the diagnosis of hypertension sets an arbitrary threshold; mechanisms that control BP are not substantially different in those with normal versus chronically elevated BP; cardiac output and vascular response to changes in output need to vary with conditions; stress responses differ from homeostatic, resting responses

Mechanisms of BP control (resting state): major influence is volume in the system (cardiac preload); there are other integrative mechanisms, most notably the sympathetic nervous system; modulates preload, afterload, and flow redistributions; structural changes in vasculature accompany aging and chronic hypertension; physiologic systems that further modulate these responses include the renin–angiotensin system, a modulator of sympathetic nervous system outflow in those in whom this system is activated; there is marked heterogeneity in activity of the renin–angiotensin system; largely turned off in blacks compared with whites; atrophies over time; those in eighth decade of life have much lower activity; has implications for drug responses; renin–angiotensin system is controlled by sympathetic nervous system and exerts positive feedback on it; aldosterone is the most important of the adrenal steroid hormones in BP regulation; release of aldosterone chronically not very dependent on ACTH or angiotensin II; aldosterone is largely a potassium regulatory hormone that also controls renal sodium excretion; BP homoeostasis is balance between volume or preload forces and vasoconstriction or afterload forces

- Cardiopulmonary baroreflex arc: heart is principal volume sensor of body through atrial and ventricular stretch mechanisms and direct afferent control of sympathetic efferent activity; when heart changes its stretch, there is a direct and immediate neural arc that adjusts amount of vasoconstriction in peripheral organs; there is a dynamic continuum between volume, which by expansion tends to suppress the activity of the sympathetic and renin systems, and control of the afterload itself
- Hydration status: with hydration, sympathetic nervous system turned down; causes vasodilation that promotes diuresis; when sufficient diuresis and pressure and volume go down, then signal sent to brain from the heart to limit water loss; vasoconstriction occurs; with dehydration, signals sent to brain turn on sympathetic nervous system, constricting renal afferent arterioles and limiting blood flow to organs; volume-vasoconstriction continuum has implications for treatment of hypertension
- Vasoconstriction: hypertension has been characterized as a syndrome of generalized peripheral vasoconstriction, but important to consider vasoconstriction in relative sense; consider if appropriate activity of renin–angiotensin, sympathetic nervous system, and other vasoconstrictive mechanisms with reference to preload conditions for heart
- Vasodilators: similar to response to dehydration; with, *eg,* hydralazine, vasodilatation and decrease in pressure elicit a sympathetic nervous system response and secondary renin–angiotensin system response; will attempt to return BP to pretreatment baselines; called pseudotolerance; with chronic hydralazine therapy, body resets at higher level of activity of sympathetic nervous system and renin–angiotensin system, reflex renal vasoconstriction, and net antidiuresis; to sustain response, have to give an antineurohumeral agent, sympathicolytic or anti-renin–angiotensin drug, and diuretic, standard triple therapy
- Momentary stress response: any momentary stress response, whether metabolic, physiological, or psychophysiological will supersede this balancing system and BP will increase to expedite blood flow to organs with most need; patterns vary with stressor; can confound treatment attempts; in chronic hypertension, the volume vasoconstrictor homeostatic axis is operational, but whole system reset at higher level; inappropriate level of volume or vasoconstriction given BP elevation; both volume and vasoconstriction are inappropriate; with sympathetic nervous system, must consider cardiopulmonary and arterial baroreflex systems, whose purpose is largely to blunt acute changes; neither of these negative inhibitory systems, baroreflexes, can fully suppress sympathetic nervous system; over a long time, sympathetic nervous system activity goes up, volume in system doesn't go down, and result is chronically higher BP, although acute BP homeostatic mechanisms can still operate; this is baroreflex resetting, and once it has occurred, it is impossible to go back to former state
- Simple hemodynamic perspective: limited view, because BP is not just product of flow and resistance as in Ohm's Law model where flow and resistance are steady; system is pulsatile; think of hypertension as inappropriate flow and inappropriate resistance; both controlled by sympathetic and other systems; further modified by chronic structural change
- Structural changes: with aging and exacerbated by hypertension, changes in the peripheral circulation include arteriolar hypertrophy, which persists and leads

to chronic increases in resistance and, most important in elderly, increases in large artery stiffness

Systolic pressure: vicious cycle of aging, increasing systolic BP, and increasing arterial stiffness; systolic BP and arterial stiffness reinforce each other, leading to linear increase in systolic BP with age; about 0.6 to 0.8 mm Hg per yr, beginning in childhood; can plot trajectory from pediatric growth and development charts and anticipate later BP

Diastolic pressure: more complex; increases in proportion with systolic at about same rate until middle age, then abruptly begins to decline at similar rate; happens because physical attributes of arterial stiffness are superimposed upon basic flow resistance pathophysiology;

Patterns: lifetime burden of hypertension impacts rate of stiffening of arteries; factors that contribute to increased stiffening tend to further increase systolic pressure; around age 75, most have much higher systolic BP; about 150 mm Hg; tremendous impact on arbitrary fixed cutoffs for BP; in elderly, if targets are low, then all have hypertension; reason for creation of "prehypertension" category in Joint National Committee(JNC)7 guidelines; clinical signs with chronic arterial stiffness high systolic BP and low diastolic BP; pulse pressure (systolic minus diastolic pressure) is increased; typical 30-yr-old may have hypertension pressure of 140/100, but 80-yr-old may have 170/60; mean pressures are similar; also increased variability of systolic BP for physical reasons

Implications: difficult to assign appropriate BP targets because of changes with aging; if diastolic is going down with treatment, must watch closely for signs of hypotension

Arterial stiffness: intrinsic resistance to distension of artery walls; defined by ratio of increase in arterial volume or diameter, divided by change in pressure between 2 points; stiffness governed by thickness of arterial walls (arteriolar hypertrophy), collagen content, which tends to increase with age, and distending pressure within artery; also inversely related to diameter; small arteries are stiffer than large arteries; stiffness and impedance increase with distance from the heart; leads to pulse pressure amplification; systolic BP taken in arm is greater than BP at aortic root; in tall, thin, individuals, usually men, greater pulse pressure amplification caused by greater length of individual tends to cause arterial cuff BPs to overestimate central aortic pressure; called spurious systolic hypertension

Measurement: for research, can measure arterial stiffness by measuring velocity of pressure wave as it moves from central to peripheral, but not necessary clinically

Effects: arterial stiffness is not just widening of pulse pressure and systolic increase, but fact that increased pulse pressure, enhanced by pulse pressure amplification, will damage parenchyma of peripheral organs; it is believed it is barotrauma that disrupts microcirculation; increase in central and microcirculatory pulse pressure associated with microscopic arteriolar hypertrophy in older hypertensive individuals; also capillary dropout and organ dysfunction; reason why wide pulse pressure tends to lead to such consequences as reduced cognitive function through cerebral arteriolosclerosis and reduced renal function through first, renal arteriolosclerosis and subsequently, glomerular tuft dropout; glomerular filtration rate will tend to go down faster with age in people with hypertension than those without

Variability: variation in blood pressure within individual is necessary to meet demands of physiologic, metabolic, and psychosocial stresses; are regular patterns of variation, *eg*, diurnal; daytime BP is generally greater than nighttime; day-night difference(nocturnal dipping) is part of diagnostic pattern; only available with 24-hr ambulatory BP monitoring; failure of BP to decrease overnight is significant cardiovascular risk factor; overall lifetime burden of BP increased

Variation between individuals: people may have very different patterns of variability; primary reason probably arterial stiffness; if artery is stiffer, systolic will vary more than diastolic, which becomes fixed; fundamentally untreatable; when stress responses are superimposed upon this stiff artery structure, BP response to stress is exaggerated; why many older patients with wider pulse pressure, higher systolic, and lower diastolic pressures demonstrate more variability of systolic pressure; home and ambulatory BP values valuable to show patient BP not always high; in this context, high readings should not be used as targets for treatment

Target organs: lecturer distinguishes 2 categories of end-organ effects; hypertension-attributable means direct effect of BP on heart and blood vessels; hypertension-exacerbated is atherosclerotic disease

Hypertension-attributable: target organ damage includes cardiac diastolic dysfunction (stiffening of heart), and heart failure with preserved ejection fraction; cardiac stiffening occurs in parallel with macrovascular stiffening; patients with arteriosclerosis, stiff arteries, tend to have more strokes, both ischemic and hemorrhagic; microvascular complications linked to macrovascular; diseases such as progressive chronic kidney disease, cognitive impairment and dementia, and impaired vision are direct complications probably more closely related to hypertension burden and mechanical damage than to humoral factors

Hypertension-exacerbated disease: atheromatous disease, including angina, myocardial infarction, and peripheral arterial disease, effected primarily by cholesterol oxidation and dysglycemia and diabetes; most common clinical trial end points are atheromatous end points; should not be surprised if there appears to be a lesser impact of hypertension; research populations have been preselected for susceptibility and degree of severity of atheromatous disease

Healthcare consumption: hypertension is near top of list for healthcare consumption; 40 million primary care office visits annually; 3.7 million hospital clinic visits/yr; mortality rate about 300 per 100,000 attributable to hypertension; 0.3%/yr, 3% in 10 yr; about 1 out of 3 people with hypertension will die from unrelated causes; leading causes of death in people with high BP are heart disease, hypertension, stroke, cancer, and diabetes; renal deaths are about 0.1% annually; these figures based on older definitions of hypertension; 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline drops threshold to 130/80; US adult prevalence of hypertension almost 47%

Guidelines

Overview: considerable variability in guidelines year-to-year and across organizations; skepticism warranted; no guideline should replace true expert opinion or appropriate judgment; impacts on people, including providers, insurance companies, and patients; in most areas, local standards of practice are used to judge appropriateness of care; local insurers, practices, HMOs, physician groups can modify guidelines

Evidence-based medicine: concept relies heavily on results of clinical trials; need to understand limitations of each level of evidence, basic science, clinical observation, epidemiological studies, metaregression, and clinical trial information; each has limitations

Problems with clinical trials: (lecturer designs clinical trials); biases are subtle, but pervasive and important; understanding can help untangle apparent differences in results and interpretation

Controlled experiments: not closely related to real life

Confounding: composite end points are problematic; typically, have heart end points such as myocardial infarction, but also stroke or kidney disease or heart failure; these may result from different mechanisms; a population at risk for cholesterol oxidation may demonstrate a relatively lower impact of hypertension because of the greater prevalence of occlusive atheromatous coronary disease; many predictor variables are confounded, such as age, systolic BP, and arterial stiffness; when this occurs, must stratify for these variables or use sophisticated statistical techniques; important effect of population heterogeneity; interacts with confounders; consider inclusion and exclusion criteria in evaluating study results, which may be extremely divergent among different populations

Summary: absence of evidence is not evidence of absence of benefit; results of study only applicable to population in which study was done; clinician should ideally understand basic science mechanisms thoroughly and make sure that data derived from studies are congruent with observational and epidemiological data, which are further congruent with results of clinical trials; lecturer reemphasizes importance of expert interpretation

Guidelines

JNC 7: lecturer involved in developing guidelines; issued in 2003; in force at least until 2013; based on Antihypertensive Lipid-Lowering Heart Attack Trial (AHLLHAT); compared calcium channel blocker (CCB) to angiotensin II converting enzyme (ACE) inhibitor to diuretic, diuretic arm of trial overweighted in terms of allocation; had alpha blocker arm but alpha blocker therapy was discontinued because it caused edema and possibly heart failure; primary outcome of fatal and nonfatal myocardial infarction (MI) was virtually identical with diuretic, CCB, and ACE inhibitor; investigators concluded that diuretics were superior based on cost and side effect profile; neither was primary endpoint of trial; lecturer describes disagreements between government and expert panel regarding content of guidelines and stands by those eventually issued

JNC 8: began 2005, 2 yr after JNC 7, released 2013; based on ACCORD (Action to Control Cardiovascular Risk in Diabetes) study (2005), which was designed to investigate whether markedly lowering systolic BP reduces cardiovascular events in patients with Type II diabetes; 4700 patients with type II diabetes assigned to receive intensive treatment regimen to lower BP below 120; compared to standard BP target; used primary composite outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular disease; after 1 yr, intensive group was at 119 systolic BP and regular group was at 133; annual composite outcome rates were relatively low and not different; stroke rates were about 40% lower with intensive therapy; adverse events rates were higher; concluded that treating to 120 or less did not reduce fatal and nonfatal cardiovascular disease (CVD) events in this population; controversial statement made by JNC 8 group that BP threshold should be increased to 150 over 90 in people over age 60; based on lack of evidence of benefit (*ie*, no studies had been done that showed benefit) of lower BP in this group; but perception developed that unnecessary to treat people over 60; in guidelines, only 30 trials cited of 785 conducted during the relevant period; though supposedly evidence based, 6 of 11 recommendations were based on expert opinion, not data from clinical trials; in 2013, NIH withdrew sponsorship; Some JNC 8 panel members published independent report (not officially JNC 8); some on JNC 8 panel published dissenting report objecting to increasing hypertension threshold to 150/90 in elderly; subsequently, the American Association of Family Physicians and the American College of Physicians incorporated the "JNC 8" recommendations into their own guidelines, and this approach is reflected in the American Board of Internal Medicine board exams for 2016 and 2017 (and their preparation materials); however, "JNC 8" has now been superseded by very different new guidelines

2017 ACC/AHA guideline: influenced by SPRINT (Systolic BP Intervention Trial) study of systolic hypertension in elderly; similar to ACCORD, testing if lower is better; did not study diabetics; used intensive therapy, target systolic BP <120 compared to usual therapy targeted to <140; used automated office BP; superior to standard office technique; yields values 5 to 10 mm lower than usual office BPs; twice as many people studied as ACCORD; roughly same outcomes in achieved BPs; composite end point included MI, coronary syndrome, stroke, CV death; also included heart failure events, rarely included in hypertension clinical trials; results of SPRINT were that lower was better largely, but not exclusively, because of reduction in heart failure events; all-cause mortality was reduced by 27%; composite outcome by 25%; however, there were higher adverse event rates, including hypotension syncope, electrolyte abnormalities, possible kidney function changes; in nondiabetic patients at high risk for CVD events, lower was better; extended this to frail elderly, who also benefitted

Other guidelines: agreement that BP measurement techniques need to be improved; evaluation is similar; similar advice on drug therapy; disagreement on hypertension classification, therapy targets, and concept of risk-stratified therapy; guidelines from Canadian Hypertension Education Program (Hypertension Canada) and from European Society of Hypertension in conjunction with European College of Cardiology are superior to US

guidelines in opinion of lecturer; issues unresolved in any of the guidelines include question of when BP is too low, age-adjusted targets, how to deal with BP variation

Differences between 2017 and prior guidelines: include measurement tools, new and highly controversial BP classification system, new treatment targets, and new recommendations for first line drugs

Measurement techniques: BP indicators are systolic, diastolic, pulse pressure, and mid pressures (mean arterial pressure, mid blood pressure); patient should be in quiet room at least 5 min undisturbed; if sitting, feet should be on floor; should not be sitting on exam table with legs dangling and back unsupported because, on average, systolic BP is 5-10 mm Hg higher; automated office BP (AOBP) helps to deal with stimulation; nobody in room; patient enters room and device or patient-activated device will supply at least 3 BP readings; 5-10 mm hg less than provider standard BP; oscillometric; systolic is reasonably accurate, diastolic is not; variations from oscillometric pressures; one reason for going away from diastolic

- Cuff size: important in some people; 35 cm arm circumference for adults, meaning a large arm cuff; mean of 3 readings and watch for variations; gives hint of BP variability
- Recommendations: feed back readings to patient; office BPs are insufficient; need home or ambulatory BP
- Comparisons: clinic BP of 140/90 corresponds roughly to home BP monitoring by patient of 135, about 5 mm difference, usually in daytime; comparing office to nighttime, home BP, can be 15-20 mm difference in systolic pressure; if higher levels of pressure, wider difference between home-derived or ambulatory BPs and office BPs; smaller difference at lower end; with AOBP, values are similar to home or 24-hr ambulatory monitoring
- White coat hypertension: AOBP ameliorates white coat artifact; white coat hypertension has lower risk profile than sustained hypertension
- Masked hypertension: home greater than office BP; lecturer's experience is that it is only an issue at the lower BP range and therefore, in the lower risk groups; white coat effect is more pronounced in those with higher BP
- Categorization (2017 guidelines): BP less than 120 systolic or 80 diastolic is normal; elevated is 120 to 129 systolic and still less than 80 diastolic; stage 1 hypertension is 130 to 139 systolic or 80 to 89 diastolic; stage 2 is 140/90 or more; very aggressive approach; no other hypertension organization agrees with this; huge numbers of people are classified as having hypertension and virtually everybody past middle age becomes hypertensive and therefore potentially requires treatment; given BP variability, trying to define categories by 10 mm windows is problematic
- Prevalence: using JNC 7 terms, prevalence of hypertension was 32%; 46% under 2017 guideline; in European guidelines, grade 1 hypertension starts at 140 systolic by standard office measurement; Canadian guidelines say hypertension begins at 140 with standard office determination, but have committed to switching to AOBP and their official cutoff is 135 with no grades or stages; Europeans have 3 grades up to 180 or greater
- Evaluation: workup is that of any new patient, including fasting glucose, blood count, lipid profile, serum creatinine, electrolytes, TSH (thyroid stimulating hormone), urinalysis, electrocardiogram; optional testing might include echocardiogram, uric acid, urinary albumin to creatinine ratio; no special screening; no automatic screening for organ damage unless there is a clear history

Therapy: in most guidelines, the first step is to begin non-pharmacologic intervention

- Lifestyle interventions: difficult to quantitate how much these can affect BP; categories are not additive and overlap; weight loss may reduce systolic BP by 5 mm Hg; healthy diet, based on the DASH study, 11; somewhere in range of 2-5 mm with salt; with salt restriction, may not find much change; some are salt sensitive, some not; about 50/50; no clinical test, although there are research protocols to determine salt sensitivity; those with low renin, the elderly and blacks, tend to be slightly more salt sensitive; increase in dietary potassium intake may yield a few mm hg; exercise alone probably doesn't affect BP much unless concomitant weight loss; alcohol effect is highly variable
- Problems with lifestyle modification efforts: if patient fails, have established negative contingency relationship; success is dependent on enthusiasm and commitment, especially of time, of provider or ability to use team approach; failure rate is high
- Medications: lecturer prefers to start drugs at beginning and instruct in lifestyle modification; not afraid to stop drugs if BP decreases enough; no real impact on death or organ damage by stopping; consider a withdrawal period after 6 mo
- Risk factor analysis: guidelines say therapy must be based on risk factor analysis; want to know risk factors, modifiable or fixed, for cardiovascular disease
  - Modifiable risk factors: current cigarette smoking, secondhand smoke, history of smoking; dysglycemia/diabetes, dyslipidemia, obesity, physical inactivity, unhealthy diet
  - Fixed risk factors: durable and robust indicators of likelihood of CVD; include chronic kidney disease; family history, including familial combined dyslipidemia, early heart attack; older age is most powerful risk factor; low socioeconomic and educational status, male sex, obstructive sleep apnea, and psychosocial stress; stress may be number one; hard to measure; may or may not be fixed risk factor
  - Addressing risk factors: risk calculation in 2017 guideline comes from the US Preventive Services Task Force; derived from Framingham risk classification; age is number one; Framingham risk score is minimally BP dependent, but this may have to do with study population; in worldwide studies, 20 mm Hg over 10 mm Hg increase in BP is associated with doubling of fatal MI or risk; theoretically, if you lower BP by 20 over 10 mm hg, there should be a 50% reduction in MI and stroke death (20 over 10 rule); not consistent with American Heart Association calculator; keeping all other risk factors constant only 10% reduction in risk; evidence of J-curve, with higher risk at highest and lowest BPs; Europeans focus on this; no J-curve in US perspective; risk scoring systems for the American, Canadian, European guidelines

are different but do include overt cardiovascular chronic renal disease and 10-yr CVD risk; different weighting of factors; US Task Force identified a 7.5% 10-yr risk as reason to intervene; increased to 10% in 2017 guideline; Canadian system, preferred by lecturer, incorporates 10-yr estimated CVD risk of 15%; equates to age over 75 or overt cardiovascular or chronic kidney disease

Interpreting risk: at the same systolic, a low diastolic is higher risk; wider pulse pressure, stiffer arteries, and possibly greater stiffness per age group; many studies demonstrate risk of low diastolic pressure on cardiovascular mortality, morbidity, acute cardiac injury, heart failure, recurrent cardiovascular accident (CVA), dementia, and all-cause mortality; not in US guideline but prominently mentioned in European

Targets: acceptable lower limit for diastolic BP is indeterminate; 60 mm is in expert opinion in ACC/AHA 2015 guideline for treatment of patients with ischemic heart disease; 70 is in ESH/ESC (European Society of Hypertension/European Society of Cardiology); studies suggest that systolic of 120 is better than 140, but side effects and negative impact occur if diastolic too low; periodically measure BP supine and standing or sitting and standing; orthostatic BPs; many older people have impaired baroreflexes, part of arteriosclerosis, and are sensitive to volume depletion; lecturer will not treat elevated systolic BP if diastolic is ≤60; advisable to write rationale in chart; 2017 guideline is to treat if 10-yr atherosclerotic CVD risk greater than 10% and BP higher than either 130 systolic or 80 diastolic; goal of therapy to keep BP less than 130 over 80

Follow-up: 1 yr if normal BP; every 3 to 6 mo if elevated; as needed if therapy is used, generally more frequently than 3 to 6 mo; often monthly at the outset

Medications: general classes of anti-hypertensive drugs that should be used as first line agents are thiazide diuretics, calcium channel blockers, and ACE inhibitors or angiotensin II converting enzyme receptor blockers (ARBs); abundant evidence of outcome benefit and relative safety with these; beta blockers used as first line by Canadians and Europeans, but not in US; US guideline says anyone more than 20 over 10 above target should get 2 drugs initially, but also say could try one if risk is low and the BP is not terribly elevated; usually waste of time, unless lifestyle modifications include substantial sodium restriction, in which case an ACE inhibitor or an ARB would be more effective than in a patient who did not restrict salt; on average, each class of drugs lowers BP about 10 mm hg, albeit with wide variation; 2 drugs equals 20 mm hg of systolic BP lowering; Canadian guideline says if AOBP >135, start with 2 drugs; Europeans say the same for grade 1 hypertension (systolic >140); Europeans suggest initial 3-drug combinations if BP is above 160

Combinations: thiazide or CCB can be combined with ACE inhibitor or ARB if necessary, never ACE plus ARB; thiazide or CCB work best in low-renin populations like the elderly and blacks; ACE inhibitors and ARBs work best in young and Caucasian populations; combinations are similarly well tolerated in all subpopulations

Therapeutic response heterogeneity: each drug class has widely varying effects in individuals in trials; have to give the drug time, generally weeks to months; response to drug is a kind of diagnostic test for the type of hypertension in individual; variable conditions can affect drug response; if person is salt loaded, an ACE inhibitor will be less effective than if patient salt depleted

Age: with those in their 70s and beyond, focus on CCBs and diuretics; in younger people, better response to ACE inhibitors and ARBs; response to spironolactone is controversial with respect to age, but can be useful

When to initiate (lecturer's view): immediately after diagnosis; 140 systolic remains rational threshold, maybe 130 if comorbidities

Thiazide diuretics: high ceiling drugs, like indapamide, metolazone, chlorthalidone, cause more natriuresis; there are loop agents that are poor anti-hypertensive drugs in part because they cause rebound anti-natriuresis in people with reasonably normal kidney function; not true of longer acting agents of the thiazide and thiazide-like classes

Aldosterone antagonists: achieve BP lowering in part through preload, that is salt and water loss over time, but effects more pronounced in those who have predominantly aldosterone or mineralocorticoid receptor-mediated hypertension or volume retention

Diuretics in general: all these diuretics potentiate other anti-hypertensive drug classes by affecting volume; all may cause hyponatremia; not uncommon in elderly; problematic with any diuretic, including spironolactone

Sites of action: thiazides cause arteriolar vasodilation; loop agents have no positive outcome studies in hypertension by themselves, even in heart failure, and do not extend life, but improve symptoms with those who tend to retain salt and water; all diuretics may cause hypokalemia, but least likely (not impossible) with spironolactone

Renin–angiotensin system blockers: include beta blockers along with renin inhibitors, ACE inhibitors, ARBs, and new renin–angiotensin receptor blocker neprilysin inhibitor class (ARNis); all block the renin-angiotensin system at different levels; BP lowering effects are similar; not additive; exception is the ARNi class (valsartan/sacubitril), which has the additional mechanism of neutral endopeptidase (NEP) inhibition, potentiation of atrial peptins, slightly greater salt and water loss, and also vasodilation; virtually all, with the possible exception of renin inhibitors, have positive outcome benefits, indirectly by changing angiotensin II; modulate sympathetic nervous system outflow; beta blockers modulate cardiac sympathetic nerve activity and heart rate; all lower BP and are beneficial in heart failure; all inhibitors of the renin–angiotensin system tend to promote higher potassium levels and can cause hyperkalemia in susceptible populations

Distinguishing features: biggest difference between beta blockers and other renin-angiotensin-aldosterone system (RAAS) inhibitors is tendency to for lower heart rate with beta blocker and slightly higher with others; ACE inhibitors have most problematic side effects, commonly causing cough and angioedema; slow trend toward ARBs and perhaps ARNis in the future; ARNis by their potentiation of atriopeptins are unique

Beta blockers: not considered useful first line agents in US and UK because don't lower central BP as well as other agents; European and Canadian guidelines have as potential first-line therapy

Calcium channel blockers: 3 subclasses; all cause same degree of vasodilation with equivalent doses; includes dihydropyridines like amlodipine, verapamil, and diltiazem; peak dose of dihydropyridines depending on agent is 10-20 mg/day; for equivalent vasodilation with verapamil, need closer to 480 mg/day and similar for diltiazem; increased doses of verapamil and diltiazem increase side effects; similar ceilings on BP; tend to cause hydrostatic edema; cause capillary transudation by dilating pre-capillary sphincters; same mechanism by which it dilates the afferent arteriole of the renal artery, increasing glomerular filtration rate; CCB-related edema is often mistaken for heart failure; CCBs are more effective with a RAAS blocker; adding RAAS blocker tends to partly ameliorate tissue edema; all dihydropyridines have positive outcome studies, but verapamil and diltiazem can suppress cardiac conduction and excitability and play havoc with cardiac electrical effects; constipation with verapamil

Other agents: use is minimized; clonidine and central agents quickly lower BP but last only short time; have many side effects; may exhibit mini-rebounds between doses; no positive outcome studies; alpha blockers only work when given with diuretic and only with patients standing up; may worsen orthostatic hypotension and have poor if any impact on BP in supine position, including nocturnal BP

Hydralazine: should be avoided as BP drug at least because of the multiple daily dose requirement; also must add diuretic and anti-neurohumoral drug; has significant lupus-like side effects; causes reflex tachycardia in some patients

Additional resources: the American Society of Hypertension developed a specialist program; certifications are granted to those who take a course; not a board certification; clinician can become a regional hypertension specialist

Suggested Reading

Brady TM et al: Management of high BP in children: Similarities and differences between U.S. and European guidelines. *Pediatr Nephrol.* 2018 Mar 28; Epub ahead of print; **Chadachan VM et al:** Understanding short term BP variability phenotypes: From concept to clinical practice. *Int J Gen Med.* 2018 Jun 22;11:241-54; **Cloutier L et al:** A new algorithm for the diagnosis of hypertension in Canada. *Can J Cardiol.* 2015 May;31(5)620-30; **Daskalopoulou SS et al:** The 2015 Canadian Hypertension Education Program recommendations for BP measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol.* 2015 May;31(5)549-68; **Marrone O and Bonsignore MR:** BP variability in patients with obstructive sleep apnea: Current perspectives. *Nat Sci Sleep.* 2018 Aug 21;10:229-42; **Muntner P et al:** Potential U.S. population impact of the 2017 ACC/AHA high BP guideline. *Circulation.* 2018 Jan 9;137(2):109-18; **Saiz LC et al:** BP targets for the treatment of people with hypertension and cardiovascular disease. *Cochrane Database Sys Rev.* 2018 Jul 20;7:CD010315; **SPRINT Research Group et al:** A randomized trial of intensive versus standard BP control. *N Engl J Med.* 2015 Nov 26;373(22):2103-16. **Whelton PK et al:** 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high BP in adults: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension.* 2018 Jun;71(6):e13-115.

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Complicated Hypertension and Special Situations in Hypertension Management

Joseph Izzo, MD, *Professor of Medicine and Pharmacology, State University of New York at Buffalo, Chief of Medicine, Erie County Medical Center, Buffalo, New York*

Resistant hypertension: defined as blood pressure that remains uncontrolled despite appropriate doses of drugs from 3 different classes, one of which is a diuretic; alternate definition — blood pressure requiring 4 or more drugs to achieve adequate control

Diagnosis: clinician must confirm the presence of treatment resistance; according to the new US guidelines, resistant hypertension would be any blood pressure that remains above 130/80; according to the worldwide guidelines, especially those from Canada and Europe, the blood pressure threshold would remain 140/90; several things could confound the diagnosis of resistant hypertension; one of these is the accuracy of blood pressure measurements and the ability of office blood pressures to accurately reflect 24-hour ambulatory values; this is most pertinent in considering the white coat effect; another common reason for apparent resistant hypertension is non-adherence to the prescribed regimen; it is difficult to prove non-adherence in many cases, but clinicians should make every effort to identify whether prescriptions have been filled or whether there are other signs of non-adherence, such as a significant history of failing to meet clinical appointments; lifestyle factors are not the determinants for resistant hypertension, but certainly excessive salt intake, obesity, and other issues may contribute; effects of other drugs may be significant; NSAIDs may have modest effects on blood pressure; some of the newer cancer chemotherapeutic agents (eg, sunitinib (Sutent))can have substantial effects on blood pressure, which can exceed 200/150, and there can be other cardiac complications; street drugs can be an enormous problem, especially those that are stimulant in nature (eg, cocaine, crack, newer designer drugs); these can be associated with immediate toxic effects on organs and severe blood pressure elevations; resistant hypertension, when it is truly present in a reliable patient with known medical history, becomes a prompt for the clinician to consider secondary causes of hypertension

Treatment: treatment of resistant hypertension includes several possibilities; first, consider adding a mineralocorticoid receptor antagonist (ie, spironolactone), because hyperaldosteronism is common in patients with resistant hypertension; a standard admonition has been to maximize diuretic therapy, but there are significant potential problems with this approach unless the patient demonstrates signs of fluid overload; excessive volume depletion can actually worsen the syndrome

Referral: for any patient with resistant hypertension, consider referral to a hypertension specialist; the American Society of Hypertension and now a subgroup of the American Heart Association (AHA) support specialist exams in hypertension — open to generalists — consult societies' websites; in general, hypertension specialists are better prepared to deal with specific issues related to hypertension than other specialists

Common causes: the most efficient way to screen for these various conditions is to identify the pattern of refractory hypertension; other signs and symptoms may be present (eg, hypokalemia), but any of these questions should prompt consideration of referral; common causes of secondary hypertension are said to be renal parenchymal disease, renal vascular disease, primary aldosteronism, obstructive sleep apnea, and drug- or alcohol-induced hypertension

Obstructive sleep apnea: may or may not by itself be a cause of hypertension; it is most commonly confounded by obesity, which is a contributing factor to relative refractoriness to drug therapy; the use of spironolactone is warranted, because obese patients are quite responsive to mineralocorticoid receptor antagonism; the case is made for primary aldosteronism where the institution of chronic therapy with spironolactone is met with marked improvement in blood pressure control; the blood pressure response in primary aldosteronism is not necessarily immediate, and patients should be instructed to wait a few weeks for the final effect to be manifested

Renal vascular disease: the treatment is largely medical; use renin-angiotensin inhibiting drugs, especially angiotensin-converting enzyme (ACE)inhibitors or angiotensin receptor blockers (ARBs); previously, these drugs were avoided based on an incorrect assumption that renal function would be worsened; today, it is generally believed that medical therapy is superior to other interventions, including renal artery stenting and other forms of renal artery surgery

Renal parenchymal disease: an obvious cause of secondary hypertension; in this case, the use of more diuretic is often met with a proportional reduction in blood pressure; there are extremes where excessive reduction in extracellular fluid volume and cardiac preload elicit a hypertensive response

Uncommon causes: there are uncommon causes of secondary hypertension; pheochromocytoma rarely exists without a family history of multiple endocrine neoplasia; Cushing syndrome is even rarer than

pheochromocytoma; relatively uncommon adult conditions include previously undiagnosed aortic coarctation or mineralocorticoid excess syndromes other than primary aldosteronism; endocrine hypertension, including hypo- or hyperthyroidism, hyperparathyroidism, or acromegaly, could contribute to high blood pressure; in general, the effects of these conditions on blood pressure are quite minimal; if a patient presents with significant blood pressure elevations, a full endocrine work-up is probably not warranted

Secondary hypertension: screening for secondary hypertension includes, in addition to checking for drug resistance, obtaining details of the onset of hypertension; especially if it occurs before age 30 and in young women, it may represent fibromuscular hyperplasia; if there is a disproportionate degree of target organ damage, a history of accelerated hypertension, or hypertensive crisis, and an increase of diastolic blood pressure in older people, the presence of hypokalemia should be sought; however, the vast majority of patients with hyperaldosteronism do not have hypokalemia; those with hypokalemia usually have large adenomas that have been present for many years

Primary aldosteronism and hypokalemia: a spontaneous potassium level of <3 should be investigated; if the patient is on diuretic, a substantial degree of hypokalemia is really the clue that you need to look for (ie, generally a potassium <2.5); adrenal masses may be discovered incidentally and may have no endocrine implications at all; in the screening for primary aldosteronism, sometimes a plasma aldosterone-to-renin ratio is done; if the aldosterone-to-renin ratio is markedly elevated (eg, >50), there is a reasonably high chance of primary aldosteronism; many recommendations of a cut-off of an aldosterone-to-renin ratio of <20 are confounded by low-renin hypertension; generally, the plasma aldosterone itself should be elevated to use this test, because renin may be far less than 1 and the ratio could be very high simply because the renin is low, whether or not hyperaldosteronism is present

Primary hyperaldosteronism: diagnosis depends on imaging studies (eg, CT or MRI); a 24-hour urinary aldosterone is a more robust diagnostic tool than the aldosterone-renin ratio

Treatment: treatment of primary aldosteronism can be adenomectomy in more specialized centers with endoscopic capabilities, or adrenalectomy; the practitioner must understand that even if adrenalectomy or adenomectomy is performed, it is highly likely that the patient will end up back on blood pressure medications; surgery removes the need for spironolactone and often reduces the number of required blood pressure medications; thus, surgical intervention may be less attractive than medical therapy; chronic medical therapy with spironolactone or amiloride is highly effective and preferable in many individuals

Renal artery stenosis: results from fibromuscular disease in young women or atherosclerotic disease in older individuals, especially in smokers; the pathogenesis and natural history should be understood, because the system changes and so does the response to drug therapy; early in unilateral renal artery stenosis, there is renin-angiotensin system activation and renin-angiotensin blocking drugs are highly effective in lowering blood pressure; revascularization may be considered, but is only the primary recommendation in young women with fibromuscular hyperplasia

Diagnosis: can be made by duplex ultrasound or more advanced imaging techniques; a disparity in renal size of 1 cm or more suggests ischemic nephropathy has developed; in this circumstance, the question often arises whether revascularization should be considered for the ischemic nephropathy itself; as far as blood pressure goes, medical therapy is still indicated

Revascularization of the kidney: the effectiveness of revascularization is difficult to predict unless one has a wedge renal biopsy and can demonstrate that 4-5 glomeruli are still fully active and normal; we don't have this in most patients, so the response cannot be well predicted, and it is difficult to make a firm recommendation for renal revascularization; by the time we see atrophy of one or both kidneys, we are typically in the later phases, where, in contrast to early, unilateral renal disease, the blood pressure no longer depends on the renin-angiotensin system; you may see blood pressure rise as renal ischemia progresses, yet responsiveness to renin-angiotensin-aldosterone (RAAS) blockers has diminished; this could be a sign to consider revascularization, but further data are required; as the kidney becomes progressively more ischemic, it also becomes less able to excrete a salt and water load; diuretics, either thiazides or loop diuretics, can be added to enhance blood pressure control; there are guidelines for revascularization that involve the attempt to prevent or improve the management of other comorbidities (eg, recurrent heart failure, flash pulmonary edema, angina, accelerated hypertension, and reduction in renal function); it is impossible to promise a patient that revascularization will eliminate the need for blood pressure medications; I recommend medical therapy for renal artery disease except in fibromuscular hyperplasia

Obstructive sleep apnea: is associated with increased sympathetic nervous activity stimulated by hypoxia; CPAP by itself does not typically help in lowering blood pressure; I suspect that the obesity of these patients is the driving factor; spironolactone and mineralocorticoid receptor antagonists are attractive alternatives, as is the combination of spironolactone with thiazide diuretic or with chlorthalidone, indapamide, or metolazone; these drugs are often more effective in obese individuals

Hypertensive emergencies: hypertensive complications that constitute true emergencies include angina or acute MI, acute decompensated heart failure or pulmonary edema, ischemic stroke or subarachnoid hemorrhage, hypertensive encephalopathy, aneurismal dissection or rupture, or preeclampsia/toxemia; these are evidence of acute organ damage

Definition of a hypertensive emergency: the patient has markedly elevated blood pressure, generally above 180/100, in the presence of acute organ damage; markedly elevated blood pressure alone, even with systolic >200 or diastolic >140, does not constitute a hypertensive emergency in the absence of acute target organ damage

Hypertensive urgency: some people have defined a lower-grade condition of hypertensive urgency to encompass the group with marked blood pressure elevation alone; you should not have your staff send the patient to the emergency room or consider admitting the patient to the hospital simply because the number is high

Treatment: in cases of elevated blood pressure without acute end-organ damage, start or restart oral therapy with 2 or 3 drugs immediately and ensure outpatient follow-up within 3 days; far too often, the office staff sends patients to hospitals or emergency rooms that should not be there; if there is a true hypertensive emergency, an emergency room visit and an ICU admission is highly appropriate; the ICU is necessary because monitoring has to be close, and parenteral drug therapy will also be required

Pathophysiology: when blood pressure is very high, and especially in hypertensive urgencies and emergencies, the hemodynamic profile is typically one of marked peripheral vasoconstriction and usually fairly severe volume depletion; accelerated hypertension is a situation where preload and volume are down; blood volume reductions are typically in the region of 30% in individuals with hypertensive urgencies and emergencies because of the chronic effect of pressure diuresis; it has been seen in various forms of secondary and accelerated hypertension, including renal artery stenosis, pheochromocytoma, hyperaldosteronism, and can be true in those individuals who have refractory hypertension of unknown etiology; in these individuals, because of vasoconstriction, reduction in blood pressure depends on adequate vasodilation, most often labetalol, and simultaneous sympathetic nervous system suppression, because the sympathetic nervous system is over-activated by chronic volume depletion; in some individuals where there is difficultly achieving blood pressure control, a paradoxical blood pressure response to volume loading or depletion is occurring; people who are markedly volume depleted have marked activation of the blood pressure defense mechanisms (ie, the sympathetic nervous and renin-angiotensin systems); clinical signs of volume contraction should be sought (eg, excessive thirst, postural blood pressure decreases, unexplained tachycardia, excessive increase in heart rate on standing, increase in urine concentration with high specific gravity, or a low urinary sodium); if these signs are present, avoid intensifying diuretic therapy or adding a loop diuretic, because it may worsen blood pressure; third-world literature recommends saline infusion for the treatment of accelerated hypertension, and I do this in patients who are clearly volume depleted; it only works over the short term, but can be an important adjunct to therapy in these individuals on the way to more appropriate individualized therapy or intensified triple therapy; an ICU is appropriate for a true hypertensive emergency; drug therapy varies depending on comorbidities and the etiology; the safest and most effective of all agents is labetalol given intravenously or intramuscularly; under conditions of ischemia, nitrates should be considered; consider acute inhibition of the renin-angiotensin system if you know there is angiotensin-dependent renal artery disease; in these circumstances, there is no contraindication to use of labetolol; loop diuretics can be used if there is clear-cut fluid overload, renal failure, or heart failure; be careful to look for the possibility of severe volume depletion

Complicated management algorithms: how fast to lower blood pressure depends on the nature of the hypertensive crisis; for severe aortic disease with dissection, blood pressure should be reduced to <140 systolic during the first hour and then as soon as possible to <120; for adults without something as immediately blood pressure sensitive as aortic disease, longer time can be taken, and a first plateau would be around 160/100 within 2 to 6 hours; there are situations where it may be wise to go even more slowly than that, such as patients with stroke, as opposed to intracerebral hemorrhage; stroke must be differentiated from hemorrhage; if there is intracerebral hemorrhage, a continuous infusion drug should be used and systolic pressure should be lowered to <140 within a few hours; a systolic blood pressure of 150-220 is not a benefit in these individuals, but is in acute ischemic stroke; in the setting of ischemic stroke, blood pressure should be lowered much more slowly; for a patient who is eligible to receive intravenous tissue plasminogen activator (TPA), the blood pressure should be initially stabilized in the range of 180 to 200 over about 110; a specific recommendation of 185/110 is generally made prior to the initiation of thrombolytic therapy; over the next 24 hours, it is advisable to lower blood pressure to as low as 140/90 if the patient is neurologically stable and the general condition warrants; if a patient comes in with a blood pressure of 220/120 or greater and TPA or endovascular treatments are not being considered, blood pressure should be lowered by 15-20% during the first 24 hours; my opinion is that the more important recommendation is to go by the clinical assessment of the physician

Blood pressure targets for patients with comorbidities: 130/80 is the threshold for diagnosis of hypertension and the blood pressure goal is <130/80 in anybody with clinical cardiovascular disease (CVD) or a 10-year atherosclerotic CVD risk of more than 10%, according to the 2017 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines; no matter what the comorbidity (eg, diabetes, chronic kidney disease, renal transplant, heart failure, ischemic cardiac disease, secondary stroke prevention, or peripheral arterial disease), the blood pressure goal is stated to be <130/80; depending on how old the patient is and how stiff the patient's arteries are, these goals may not be wise; if a patient has a wide pulse pressure (eg, 160/70), it may not be wise to lower blood pressure further, even though we would like to do so, because of the risk of diastolic hypotension; diastolic hypotension and the cut-off of 70 diastolic are prominent features of the European guidelines but are absent from the US guidelines; Canadian guidelines suggest that the physician be aware of and on guard for hypotension and state that hypotension may be a limiting factor for further therapy; in the American guidelines, insufficient attention is paid to this possibility; but there is ample evidence that each of these comorbidities may

be worsened by very low diastolic pressure (ie, the outcomes in these groups are worse)

Cardiac comorbidities: the target of <130/80 is appropriate for patients with stable ischemic heart disease, stable heart failure, and preserved or reduced ejection fraction

Heart failure management: the most effective drugs in heart failure are blood pressure drugs; the limiting factor is usually hypotension; complications may be iatrogenic; important example is acute kidney injury (AKI), not to be confused with real cardiorenal-syndrome renal failure; patients with hypertension and heart failure may demonstrate greater variation in serum creatinine as a result of variations in blood pressure and tissue perfusion; this is often conflated and confounded with a change in serum creatinine that is not indicative of anything other than what used to be called prerenal azotemia; the mischief that arises from calling hypoperfusion AKI is that necessary cardiac drugs are often withheld when there is no need to do so; the whole concept of AKI is sketchy at best, and the small changes in serum creatinine (as low as 0.2 mg/dL) defining this syndrome are statistically and scientifically ludicrous; consider strongly that unless compelled by anuria or rapidly increasing serum creatinine of 1 to 2 points per day, suggesting GFR of 0, don't fool around with the heart failure drugs; what needs to be changed more commonly is the diuretic; this is not to say that a cardiorenal syndrome cannot exist, in which it becomes increasingly difficult to achieve diuresis in patients with hypoperfusion of the kidney due to low cardiac output, but this is a separate topic; as long as the patient is urinating and responding largely to diuretic therapy, we should not superimpose some idea that there's kidney injury when in fact an elevation in creatinine is a simple hemodynamic event; in heart failure management, several principles should be observed, including control of heart rate, generally with beta-blockers; the better control we have of the renin-angiotensin and sympathetic nervous system, using renin-angiotensin blocking drugs, the lower the heart rate is; in the US, we don't tend to use the "funny" (I_f) channel blocker ivabradine, but European data indicate that it may be useful in some patients; the sweet spot of the heart rate is about 70, so we want beta-blockers; in this case, we're forced to use other RAAS blockers because we don't have a lot of information on whether ACE inhibitors or ARBs are fully necessary in patients who are fully beta-blocked before those agents are used; diuretics are also not optimally handled in this patient population; a key to success is to get ahead of the cycle of volume retention, and in order to do that, the patient has to be instructed on when to increase the diuretic; if the patient is becoming volume depleted, hold the diuretic; a period of altered diuretic dose is generally 2 to 4 days; these changes are critical in preventing unnecessary rehospitalizations; with chronic kidney disease, it's generally recommended that RAAS blockers be used, but there is very little if any information to suggest that the use of RAAS blockers in patients without hypertension does any good; the indicator of concern here is the urinary albumin excretion rate; in people with blood pressures <140/90, we have little evidence that RAAS blockade matters, suggesting that blood pressure is a primary concern; if the blood pressure is >140/90 or >130/180, one presumes that RAAS blockers should be considered as part of the management of hypertension; we use the presence of albuminuria, that is 300 mg/g of creatinine or 300 mg/day, as an indicator of chronic kidney disease (CKD), often diabetic kidney disease; this is primary target group for therapies discussed

CKD classification: renal function tends to decline with age as a statistical average in the population, but this is not necessarily true on an individual basis; many people have stable renal function over decades; the use of estimated glomerular filtration rate(eGFR) caused us to go from a situation where we under-recognized renal disease to one where it is now grossly over-recognized to the point of artifact and consternation among patients and providers; stage 3 CKD, (ie, an eGFR <60) is not a strong indicator of progression to end-stage renal disease; eGFR is just an adjusted reciprocal of the serum creatinine; embedded in eGFR is the assumption that renal function declines with age, when in fact, it may or may not in a given individual; in stage 4 CKD, those patients well may progress to end stage disease; that's not true for the differentiation between stage 2 and stage 3; more recent clarifications indicate that the presence of albuminuria is more prognostically significant; also think about both nephritis and nephrosis; get a urinary sediment; look for cells and casts; nephrosis is largely proteinuria; people with hypertension can have a variety of different renal diseases but these are actually quite uncommon; hypertension rarely progresses to marked nephrosis with nephrotic syndrome, but that can happen in diabetics; eGFR is a really poor tool for discrimination; unless there is albuminuria or evidence of an active urinary sediment or a dramatic quick change in the serum creatinine, it's unlikely that these patients have any meaningful level of disease; Most of the time, renal function is stable; it varies with hydration status and drugs; to lower creatinine (or the eGFR), give ACE inhibitors; eGFR goes down because the intraglomerular pressure goes down; to raise eGFR, give a calcium channel blocker because arteriolar dilation increases glomerular filtration; changes like this are substantial and can often be 10-20% in either direction; if the blood pressure goes down, the eGFR goes down as a rule; this is primarily pressure- and flow-related; if you're approaching stage 4 CKD, that's the time to refer to the nephrologists; one of the most important reasons is to consider whether treatment for the underlying condition is necessary, but the most important thing is to begin to consider whether dialysis access is necessary; it takes some weeks for a fistula to mature; the longevity of dialysis patients who have fistulas is far greater than those forced to dialyze through a catheter; one of the reasons to consider referral is to preserve adequate vascular access, because often the rate-limiting step for mortality in dialysis patients is limited or poor vascular access; in transplant patients, calcium channel blockers (CCBs) are appropriate agents because of the low-grade vascular toxic effects of some of the anti-rejection drugs and the ability of CCBs to help ameliorate this problem

Secondary stroke prevention: there does not seem to be a J-curve with respect to recurrent stroke; in this context,

there are fairly clear-cut follow-up studies suggesting that lower blood pressure really is better down to the level of 110 or so systolic; this is a bit surprising given the nature of the condition, but it may also demonstrate how closely stroke is related to blood pressure; in these individuals, it is important to monitor therapy; aggressive blood pressure therapy to targets <130/80 is warranted for preventing recurrent strokes, but may not be tolerable in elderly individuals

Diabetes: patients with diabetes present certain challenges; the progression to end-stage renal disease attributable to diabetes in most of the literature is probably due to blood pressure interaction with the diabetic kidney; there is no reason to avoid calcium channel blockers or diuretics in these individuals; the triple combination of diuretic, CCB, and RAAS blocker is often required to achieve the blood pressure target of 130/80 or less

Peripheral arterial disease: is not that common, but is found along with coronary and cerebrovascular disease; the blood pressure target is generally 130/80; beta-blockers are not contraindicated; often, atrial fibrillation lowers blood pressure because it lowers cardiac output; generally not a problem in terms of hypotension; one study indicated that ARB use limited new development of atrial fibrillation more than prior beta-blocker use

Dementia and cognitive decline: one of the strongest predictors of cognitive impairment is hypertension in middle life; people who are effectively treated for hypertension appear to have a reduced prevalence of cognitive decline and dementia in later life; it is not completely clear which agents are better; some European data with calcium channel blockers suggest that dihydropyridines may be the preferred drug class; CCBs may look better because patients are elderly, and blood pressure was actually better controlled with these agents than with beta-blockers or renin-angiotensin inhibitors; this is another situation where "lower is better" is probably appropriate

Other special groups:

Pregnancy: some of us treat pregnant women with hypertension, and the chronic maintenance generally hasn't changed too much; in addition to methyldopa, dihydropyridine and labetalol are now considered reasonable drugs; diuretics are generally avoided, and renin-angiotensin system blocking drugs are generally contraindicated (ie, ACE inhibitors, ARBs, renin inhibitors) because of teratogenic and untoward effects on the fetus;

Surgical patients: in patients with planned elective major surgery and a systolic of 180 or higher or diastolic of 110, surgery is often deferred; I see patients commonly who have white-coat hypertension or highly variable blood pressure where the misdiagnosis causes the deferral of surgery even when it's required; these patients have blood pressures that are highly responsive to general anesthesia, and a competent anesthesiologist can largely dial in any pressure that she or he wants; in our center, we are used to major trauma care and our anesthesiologists are not frightened by blood pressure elevations, either too low or too high; I encourage frank discussion with anesthesiologists; appropriate blood pressure control by the internist is warranted, but in some cases it has been difficult for patients to obtain necessary surgery; I think it is a rare case in which the necessary surgery should be withheld because of blood pressure; beta-blockers should be continued through the preoperative period, but not started on the day of surgery; withhold other antihypertensives the morning of surgery as long as those drugs are reinstituted immediately after surgery; in the operating room, blood pressure control is not difficult to achieve; parenteral agents are sometimes, but not usually, required; generally speaking, blood pressure control in the perioperative period is not very difficult

Suggested Reading

Heimark S et al: Which target blood pressure in year 2018? Evidence from recent clinical trials. *High Blood Press Cardiovasc Prev* 2018 Jun;25(2):151-8; **Paini A et al:** Definitions and epidemiological aspects of hypertensive urgencies and emergencies. *High Blood Press Cardiovasc Prev* 2018 Jun 18 [Epub ahead of print]; **Wei FF et al:** Diagnosis and management of resistant hypertension: state of the art. *Nat Rev Nephrol* 2018 Jul;14(7):428-41.

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Dyslipidemia and Large Artery Disease

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Overview: lipids play central role in atherosclerosis; deposition in sub- and intimal space within arterial wall — initiating step of atherogenesis; lipid deposition triggers inflammatory response, leading to subclinical atherosclerosis — sets stage for atherosclerotic cardiovascular disease (CVD) events; management critical to treating atherosclerotic CVD risk

Overview of lipids and lipoproteins: cholesterol and triglycerides fundamental to physiological processes; insoluble in plasma; lipids carried in lipoprotein particles

- Types of particles (from largest to smallest): chylomicrons and chylomicron remnants; very large dense lipoproteins, (VLDL) and its remnants; intermediate-density lipoproteins (IDL); low-density lipoproteins (LDL); lipoprotein(a) (Lp[a]), which is similar to LDL particle; high-density lipoproteins (HDL); sizes of each of these particles can vary substantially, both within individual and among individuals
- Particle content and roles: triglyceride-to-cholesterol ratio varies; majority of triglycerides carried in larger particles, including VLDL and chylomicrons; majority of circulating cholesterol typically carried in lower-density lipoproteins, mainly LDL particles for most people; lipoproteins shuttle lipids throughout body; guided by interactions between proteins on surface with circulating enzymes
- Apolipoprotein B (ApoB): primary surface protein for all but HDL particles; in 1:1 ratio on surface of chylomicrons, VLDL, IDL, LDL and Lp(a); confers atherogenicity; retention of ApoB particles in arterial wall; HDL particles do not have ApoB on surface; instead of 1:1 ratio of ApoB-containing particles, HDL particles have apolipoprotein A in various concentrations, ranging from 1 to 4 or more
- Lipoprotein pathways: 2 primary pathways responsible for shuttling lipids
  - Exogenous: refers to intestinal absorption of cholesterol and fatty acids; results in chylomicron formation — largest lipoprotein particles; contain large amount of triglycerides; lipoprotein lipase acts on chylomicrons in circulation; generate free fatty acids from internal triglycerides — used for energy or stored in adipose cells; chylomicron remnants rapidly cleared by liver; happens quickly after meal; reason for fasting lipid measurement recommendations in past
  - Endogenous: synthesis of VLDL particles by liver; acted upon by lipoprotein lipase and hepatic lipase to form VLDL remnants, IDL particles, and then LDL particles; LDL receptor on hepatocytes takes circulating LDL back into liver
- Serum lipoproteins: LDL — dominant circulating lipoprotein in most people; primary atherogenic lipoprotein, particularly when oxidized; smaller LDL particles more likely to penetrate endothelium; non-HDL,or total cholesterol minus HDL, reflects circulating cholesterol contained in ApoB-containing lipoproteins; triglycerides can be considered measure of larger particles, including VLDL, chylomicrons, and remnants
- Epidemiology: higher serum LDL particle concentrations — represented by high ApoB levels, high particle-concentration measurements, or higher LDL levels associated with higher risk for atherosclerotic disease; higher HDL levels inversely associated with atherosclerotic disease risk

Lipid-lowering therapy: focused on reducing circulating ApoB-containing lipoproteins, principally LDL; HDL particles heterogeneous; capacity for mediating removal of cholesterol from peripheral macrophages for reverse cholesterol transport to liver; efforts to increase HDL have not reduced events; focused on capacity for HDL efflux — removal of cholesterol from macrophages

Measurement: standard lipid profile useful for >50 years; in fasting state, circulating blood lipoproteins predominantly VLDL, LDL and HDL; in standard lipid profile, total cholesterol concentration, HDL concentration, triglycerides directly measured

- Friedewald equation: uses triglycerides to estimate cholesterol content of VLDL particles; when triglycerides <400 mg/dL, Friedewald found average 5:1 ratio of triglyceride to cholesterol in VLDL particles; ratio different when triglycerides >400 mg/dL; direct measurement of LDL recommended in such cases; in standard lipid profile, when triglycerides <400, LDL estimated by taking total cholesterol minus HDL minus estimated VLDL, or triglycerides, divided by 5
- Novel approach: recent work using direct LDL measures found 5:1 triglyceride-to-cholesterol ratio in VLDL particles can vary even when triglycerides <400; method of estimating LDL using adjustable ratio of triglyceride to cholesterol increasing
- Fasting or nonfasting: varying recommendations; total cholesterol and HDL, by extension non-HDL cholesterol, not significantly affected by fasting; triglycerides can vary markedly due to fasting; can lead to variation in VLDL and LDL estimates; with guideline changes, nonfasting samples increasingly acceptable

Definition: in general, dyslipidemia considered any abnormal elevation in total cholesterol, LDL, non-HDL, ApoB, Lp(a), or triglycerides; could be abnormally low levels of HDL

Management of Dyslipidemia

Overview: principal component — lifestyle modifications, regardless of pharmacotherapy; cessation of tobacco use; regular physical activity; maintaining healthy weight

Evidence-based dietary guidance: focus on DASH diet or Mediterranean dietary patterns; emphasize limited sugar or simple carbohydrate intake; limit red meat; replace saturated with polyunsaturated fats; increase fruits, vegetables, whole grains, and high-fiber foods; lean meats (*eg*, poultry, fish) preferable to red meat; dietary changes led to >10 mg/dL reductions in LDL; aerobic exercise also led to slightly lower LDL reductions

Pharmacotherapies: statins — primary therapy for 2 decades

Mechanism: block critical step in cholesterol synthesis in liver — increase expression of LDL receptors on hepatocyte surface, leading to removal of more LDL particles from circulation

Evidence: many event-driven trials comparing high-intensity with low-intensity statin, or statin vs placebo; summarized by analyses from Cholesterol Treatment Trialists' Collaboration; main criteria for inclusion in studies — randomized, >1000 participants followed for at ≥2 years for events, and author access to participant-level rather than study-level data; 2010 meta-analysis included 26 statin trials with long-term follow-up — participant-level data from nearly 170,000 participants; included 5 trials of nearly 40,000 individuals comparing high- vs low-intensity statins and 21 trials of nearly 130,000 participants comparing statin vs placebo; main endpoints — cardiovascular (CV) mortality, revascularization, myocardial infarction (MI), stroke; primary finding — statins associated with linear reduction in events proportional to degree of LDL reduction; ~40 mg/dL reduction in LDL associated with 20% relative risk (RR) reduction in MI, revascularization and ischemic stroke, and 10% RR reduction in all-cause mortality, mainly from reduction in coronary heart disease death; general RR reductions held true in subsequent analyses for men and women across categories of baseline LDL levels, including at lower LDL levels, and across categories of baseline risk, including low-risk groups

Guidelines

2013 Guidelines: 2013 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines controversial; shift from surrogate targets (*eg*, LDL) to focus on evidence for reducing outcomes and events; prior guidelines focused on LDL targets correlating to risk; high-risk patients recommended to achieve LDL <70; secondary target non-HDL cholesterol levels <100 in highest-risk patients; those at low or moderate risk for atherosclerotic cardiovascular disease (ASCVD) recommended to achieve less aggressive targets, such as LDL <100 or <130

Issues considered in 2013 guidelines: multiple trials have established statins as principal pharmacologic therapy in primary and secondary prevention of ASCVD in terms of reducing events and LDL; trials comparing statin with placebo and high- to lower-intensity statins showed improved outcomes with higher-intensity statin treatment, proportional to degree of LDL reduction achieved; degree of LDL reduction may be surrogate for intensity of treatment; CETP inhibitors lowered LDL and raised HDL but did not change CV event rates; torcetrapib led to increased risk; studies of niacin plus statin therapy showed no impact on CV events in patients with low LDL levels on statins

Additional considerations: absence of trial testing treat-to-target approach to LDL reduction to reduce outcomes; no specific trials test target LDL levels; meta-analysis suggesting lower LDL is better took RR approach; risks of statin treatment include increased blood sugar (hyperglycemia) and cost; 2013 guidelines focused on absolute risk-benefit ratios

2013 recommendations: controversy because of shift to risk-based decisions not cholesterol targets, prioritized statins; drafted 4 statin benefit groups among adults

First group: prior clinical CVD including known obstructive coronary artery disease, prior MI or stroke, or known peripheral artery disease; high-intensity statin should be prioritized for those aged <75 yr; higher doses of atorvastatin and rosuvastatin shown to lower LDL by >50%; for those aged >75 yr or with contraindications to high-intensity statins, should prioritize a moderate-intensity statin; these lead to 30% to 50% LDL reductions; include lower doses of atorvastatin and rosuvastatin, and most doses of simvastatin, lovastatin, pravastatin, and pitavastatin

Second group: very high LDL levels, >190 mg/dL — familial hypercholesterolemia range; prioritize high-intensity statin therapy — use moderate-intensity statin if not tolerated

Third group: type 1 or 2 diabetes; aged 40 to 75 yr; use at least moderate-intensity statin; use high-intensity statin if 10-yr risk of ASCVD event >7.5%

Fourth group: controversial; aged 40 to 75 yr with LDL 70 mg/dL to 189 mg/dL, no history of clinical CVD, no diabetes; those eligible for statins for primary prevention expanded; calculate 10-yr estimate of risk for ASCVD events based on pooled cohort equations risk estimator; those at >7.5% risk for 10-year events should be on moderate- to high-intensity statin therapy; those in 5% to 7.5% risk group also likely to benefit from moderate-intensity statin; those with <5% risk unlikely to benefit; emphasis on shared decision making; consider risks and benefits, potential for drug interactions, and patient preferences

Strengths of 2013 guidelines: inclusion of stroke as relevant and preventable endpoint; prior guidelines focused on coronary heart disease (CHD); updated risk estimator included separate terms for African Americans and separate terms for men and women; push to emphasize statins

Recommended testing: prior to starting statins, lipid and liver profiles reasonable; routine measurement of creatine kinase (CK) no longer recommended; repeat lipids in ~3 mo to ensure adequate response; measure liver function tests (LFTs) and CK only if symptoms develop

Side effects: include myopathy, increased risk for hyperglycemia and cataracts; myopathy usually

reversible with cessation; often switch to another statin or lower dose tolerated; risk of diabetes and cataracts low overall and absolute benefits typically outweigh these risks when prescribing statins to those at sufficient baseline risk of ASCVD per guidelines

2016 guidelines: US Preventive Services Task Force (USPSTF) statement differed from ACC/AHA guidelines for primary prevention; low- to moderate-intensity statin for people aged 40 to 75 yr with no ASCVD history but ≥1 other risk factor, and calculated 10-yr risk of >10% by pooled cohort equations risk estimator; those with 7.5% to 10% estimated risk and 1 risk factor may be offered low- to moderate-intensity statin; insufficient evidence for statin recommendation for those aged >76 yr without history of ASCVD

Newer therapies: therapies have emerged since guidelines

Ezetimibe: blocks intestinal and biliary absorption of cholesterol; in placebo group, on treatment, LDL levels were ~70 mg/dL compared with 54 mg/dL in ezetimibe arm; over median follow-up of 6 yr, 6% to 7% RR reduction for combined endpoint of CV death, MI, unstable angina, revascularization and stroke; 2% absolute risk (AR) reduction; trial showed additive effect on top of baseline statin therapy for reduction in CV events with reduction in LDL achieved from nonstatin mechanism; no concerning safety signals

Proprotein convertase subtilisin/kexin type 9 (PSCK9) inhibitors: evolocumab and alirocumab; when coupled with LDL receptor and LDL particle in hepatocyte, enzyme PSCK9 leads to degradation of receptor; when PCSK9 absent, LDL receptor recycles back to hepatocyte surface to remove another LDL particle; up to 60% reductions in LDL; monoclonal antibodies; typically injected every 2 to 4 weeks subcutaneously

Trials: 2017 trial compared evolocumab with placebo in patients with history of CVD and LDL >70 mg/dL; placebo-arm LDL levels were ~86 mg/dL, compared with evolocumab arm levels of 30 mg/dL; at 2.2 yr median follow-up, 15% RR reduction in combined endpoint of CV death, MI, stroke, unstable angina, or revascularization; AR reduction was 1.5%; unpublished trial of alirocumab had similarly positive results

Benefits and drawbacks: well tolerated; most common issue injection-site reactions; main drawback — cost of $14,000/yr and challenges with insurance approval

Risk reduction: overall RR lower than expected based on degree of LDL reduction; possible attenuation of effect at lowest cholesterol levels or differences between mechanisms of action and effect on CV events between statins and other medications to lower LDL

Updates to guidelines: 2016 and 2017 updates by ACC/AHA in response to new evidence; for patients with clinical ASCVD history not achieving LDL <70 mg/dL on maximally tolerated statin therapy, suggest ezetimibe as first option; because of cost, PCSK9 inhibitor should be second consideration to add to statin; no changes to recommendations for primary prevention; bile-acid resins and niacin downgraded in usefulness — generally reserved for rare cases

Cholesterylester transfer protein (CETP) inhibitors: increase HDL and decrease LDL; none made it to market; disappointing outcome studies; exception — recent REVEAL trial testing anacetrapib vs placebo; >30,000 patients; led to modest reductions in LDL and modest RR reduction compared with placebo; anacetrapib not pursued; currently no CETP inhibitors marketed

2017 American Association of Clinical Endocrinologists (AACE) guidelines: AACE guidelines released; similar approach to prior guidelines; recommended targets for LDL, non-HDL cholesterol, and ApoB levels based on risk of ASCVD; 5 categories — low, moderate, high, very high and extreme risk; target LDL level for extreme-risk patients was <55 mg/dL; prioritize statins

Measures of Risk

Overview: measures of lipids and markers of atherosclerotic risk have been proposed beyond standard lipid profile

Triglycerides: marker of residual risk in statin-treated patients; no evidence for specifically treating hypertriglyceridemia to reduce CV events; treating triglycerides >500 mg/dL will lower risk of pancreatitis; typically achieved with fibrates and fish oil

Other measures: HDL strong inverse marker of risk but augmentation has not reduced events; other potential measures — lipoprotein particle concentrations in particle size, Lp(a), homocysteine, and high-sensitivity C-reactive protein (HSCRP); associated with risk above and beyond traditional lipid profile; no current role for routine measurement of Lp(a), lipoprotein levels, homocysteine levels, or evaluation of lipid particle size; expensive and no evidence of effective treatment based on these measurements

HSCRP: high level of CRP associated with CV risk; inflammatory component of atherosclerotic risk; trial of rosuvastatin in participants without prior heart disease but with elevated HSCRP levels showed reduction in major CV events over ~2 yr; however, no arm with normal CRP levels; unclear whether risk reduction was result of statin treatment and LDL reduction rather than CRP reduction; 2017 trial of canakinumab (interleukin-1B) inhibitor in patients with prior MI showed no reductions in LDL, but reductions in HSCRP and modest reduction in CV events; no support for general testing; may be used in intermediate-risk patients

Coronary artery calcium scoring: higher coronary artery calcium than expected may help in decision to start statin therapy; absence of coronary artery calcium heralds low risk and may be reassuring to patients averse to statins

Thoracic Aortic Diseases

Overview: artery walls are complex — inner (endothelial) lining and intimal layer, muscular media layer, and adventitial layer toward external edge; walls contain nervous innervation and blood supply, vasa vasorum; pathologies of large arteries typically involve walls; thoracic aortic diseases include aortic atheromas, acute aortic syndromes, and thoracic aortic aneurysms

Aortic atheromas: plaque formation; lipid core and inflammatory response within the wall; occur with ASCVD risk factors — smoking, HTN, age, sex, dyslipidemia; typically incidental finding on imaging modalities including computed tomography (CT) angiography, magnetic resonance angiography (MRA), or transthoracic and transesophageal echocardiography; complex, particularly risky plaques are thicker than 4 mm, ulcerated, or have mobile component that typically represents overlying thrombus on ulcerated or ruptured

plaque; risk for thromboembolism or stroke; particularly risky during intra-aortic procedures, including coronary catheterizations, insertion of intra-aortic balloon pumps, or surgeries requiring manipulation of aorta; increased ASCVD risk; use high-intensity statin and antiplatelet therapy (aspirin or clopidogrel) to reduce risk

Acute aortic syndromes: aortic dissections, penetrating ulcers, and intramural hematomas; can be life threatening; require early diagnosis and intervention; classic symptom severe tearing chest pain radiating to back; routine emergency imaging may show widened mediastinum, particularly with dissection; contrast-enhanced CT, MRA or echocardiogram usually needed to confirm; if unstable, CT preferred to aid procedural planning after stabilization; in unstable patient, echocardiography can be performed; magnetic resonance imaging (MRI) typically not useful if unstable; invasive angiography reserved for cases with planned percutaneous intervention

- Aortic dissection: most severe complication; tear in endothelial and intimal layers; leads to false lumen between intima and media — typically larger than true lumen due to lower pressure within space; tear can spread towards root or forward down descending aorta; can involve aortic branches; type A dissection involves aortic root, ascending aorta, or aortic arch proximal to left subclavian artery; type B dissection starts distal to left subclavian artery; type A acute aortic syndromes require emergent surgical intervention; high mortality; potential for involvement of great vessels of aortic arch or aortic root; involvement of root may compromise critical structures, including the valve; can lead to severe acute aortic regurgitation; propagation down coronary arteries can cause MI; spread into pericardial space can lead to tamponade; ascending dissections more common than descending
- Intramural hematomas: bleeds within media of aortic wall without clear intimal tear; may be due to small ruptures or bleeds from vasa vasorum; may be precursors for dissections; more frequent in descending aorta; require urgent surgical intervention when in ascending aorta
- Penetrating aortic ulcers: usually erosions of intima in region of atherosclerotic plaque; increased risk for intramural hematomas; more frequent in descending aorta
- Management: blood pressure (BP) control, unless hypotension present; reduce risk of expansion or rupture; use intravenous (IV) beta blockers — reduce rate pressure product and decrease shear stress on arterial wall; perform in critical care unit with invasive BP monitoring with arterial line; heart rate targeted to <70 bpm — typically closer to 60 bpm; systolic BP reduced to minimum level to maintain perfusion, near 100 mm Hg; nitroprusside added if further reduction needed; hypotension may indicate aortic root involvement with considerations for hemorrhagic tamponade, left ventricular dysfunction from coronary perfusion deficits, or severe aortic regurgitation; type A syndromes require emergency surgery unless too risky; type B may be medically managed if uncomplicated, or endovascular repairs if complicated

Thoracic aortic aneurysms: often result from medial layer degeneration; may involve root, ascending aorta, aortic arch, or descending aorta; more commonly root and ascending aorta; usually asymptomatic; detected incidentally; severe root dilation may result in diastolic murmur of aortic regurgitation or heart failure (HF) symptoms if severe

- Causes: related to weakening of medial layer; common cause with aging — hypertension (HTN) and weakening of media; size of aortic root and ascending aorta size increase over time; most associated with atherosclerosis; in younger individuals, connective tissue diseases or aortopathy-associated congenital bicuspid aortic valve disease more common; ~50% of patients with bicuspid aortic valve have dilation of aortic root or ascending aorta; ~2% of patients with bicuspid valves may have coarctation of aorta; Turner syndrome associated with higher prevalence of bicuspid aortic valves and aortopathies; other causes include vasculitis (*eg*, Takayasu, giant cell arteritis) and syphilis; genetic causes include Marfan syndrome, Loeys-Dietz syndrome, type IV Ehlers-Danlos syndrome, and familial thoracic aortic aneurysm syndrome
- Rupture: primary concern; rapidly fatal; risk increases with increasing aortic diameter; prophylactic surgery is typically indicated when risk of intervention is exceeded by risk of rupture or dissection
  - Threshold for surgery: for genetically mediated connective tissue disorders, risk increases between 4 cm and 5 cm; in pregnant women with Marfan, risk increases at 4 cm; for other, causes, *eg*, aging, threshold when root or ascending aorta >5.5 cm; for descending aorta, threshold for surgery is 5.5 cm to 6 cm; rapid expansion — increasing by >0.5 cm over 1 yr — another risk factor; for bicuspid aortic valves, threshold for surgery 5.5 cm; with other risk factors (*eg*, rapid growth, family history), threshold 5.0 cm; if patient with bicuspid aortic valve having surgery for primary indication of issue with valve (*eg*, severe regurgitation, stenosis), threshold to repair root or ascending aorta 4.5 cm
- Management: aggressive BP control, particularly with beta blockers; follow-up imaging in 6 mo; then annually, typically echocardiography; for genetic disorders, more frequent follow-up, such as twice per year, may be required if size >4.5 cm
  - Familial thoracic aortic aneurysm: autosomal dominant disorder; screen first-degree relatives; if gene known in proband, genetic testing in relatives can guide decision making about screening relatives
  - Bicuspid aortic valve: annual screening once root or ascending aorta >4.5 cm; primary family members should be tested; when possible, surgery should preserve aortic valve and replace aneurysm with graft; stent grafting by thoracic endovascular aortic repair (TEVAR) has lower morbidity and shorter hospital stays than with open repair; may be consideration for some patients

Abdominal Aortic Aneurysms (AAAs)

Overview: threshold 3 cm; risk factors — smoking, age, male sex, family history, HTN; 2014 review showed significant reduction in AAA-related mortality with 1-time ultrasound screening in men aged >65 yr; no impact on overall mortality; USPSTF recommends 1-time ultrasound screening for men aged 65 to 75 yr who have smoked ever >100 cigarettes; use abdominal ultrasound; inconclusive

data for women aged 65 to 75 yr who have smoked; very small benefit for men aged 65 to 75 yr who have never smoked; offer selectively; data suggest no benefit for women who have never smoked; annual risk of rupture (highly fatal) rises with increasing size of AAA; <0.5% annual risk for AAA >4 cm; 10% to 20% annual risk for AAAs 6 cm to 6.9 cm

Surveillance: timing depends on baseline size; annual ultrasound if <4.5 cm; twice-yearly ultrasounds for 4.5 cm to 5.5 cm

Elective repair: threshold 5.5 cm, increase of 0.5 cm over 6 mo, or with associated symptoms such as abdominal or back pain; threshold 5.0 cm in women; treatment includes smoking cessation and treating modifiable risk factors; use of statins and aspirin; control of BP and diabetes; open or endovascular aneurysm repair (EVAR) based on anatomy, preference, age and comorbidities; better short-term results with EVAR; similar long-term mortality; long-term complications, (*eg*, leaks) requiring reintervention, higher with EVAR — annual follow-up imaging required

Peripheral Artery Disease (PAD)

Overview: atherosclerosis in arteries at bifurcation of aorta or below; shares risk factors for ASCVD; notable difference — higher prevalence in women than men; coronary heart disease risk equivalent in patients at high risk for ASCVD events; treat aggressively with high-intensity statin, BP target <130/80 mmHg, and antiplatelet therapy

Screening: benefits of screening with ankle-brachial index (ABI) testing in asymptomatic patients inconclusive per USPSTF; per 2013 ACC/AHA guidelines, ABI can be used if decision uncertain about statin therapy

2016 ACC/AHA guidelines: screening reasonable in any patient aged >65 yr; in patients aged 50 to 64 yr with atherosclerosis risk factors or a family history of PAD; in those aged <50 yr with diabetes and an additional risk factor; those with known atherosclerotic disease

Symptoms: often asymptomatic; most have exercise limitations or intermittent claudication; lower-extremity ulcerations and chronic limb ischemia less common; distinguish claudication from lumbar spinal stenosis; exertional cramping and aching typical of both; spinal stenosis includes tingling, numbness, weakness — can occur with or without exercise; sitting can help both; claudication resolves within 5 to 10 min; spinal stenosis may take up to 30 min

Evaluation: examination of pulses; BP measurement in both arms — difference of 15 mm Hg suggestive of upper extremity PAD; auscultation for arterial bruits; evaluation of feet, ankles, skin; diagnosis by ABI testing; further evaluation by imaging, typically CT angiography, MRA, or ultrasound when interventions planned; obtain ABI when PAD suspected

ABI: BP cuff applied to calf; highest BP obtained via palpation or Doppler at dorsalis pedis and posterior tibialis used for each ankle; brachial systolic BP used for both arms; for each leg, ankle pressure divided by the highest brachial pressure to obtain ABI; normal ABI ranges from 1 to 1.4; with obstruction in lower-extremity arteries, pressure drops; result <0.9 defines PAD; 0.91 to 0.99 borderline; ABI >1.4 suggests calcification of arterial wall — toe-brachial index (TBI) recommended; if TBI <0.7, PAD present; exercise ABIs have improved sensitivity; recommended in patients with exertional symptoms with normal or borderline ABI results; significant PAD present if ABI decreases by 20% after exercise

Medical therapy: focus on ASCVD risk reduction and treatment of claudication symptoms; smoking cessation critical — leads to less amputations, improvements in ischemia and walking times, and better bypass patency; treatment with moderate- or high-intensity statin associated with reductions in mortality and CV events; BP targets should be <130/80 mm Hg based on 2017 ACC/AHA BP guidelines; first-line agents — ACE inhibitors, ARBs, thiazide diuretics, and calcium channel blockers; HOPE trial showed decrease in CV events with ramipril; ACE inhibitor reasonable with or without HTN; aspirin or clopidogrel reasonable to reduce CV events; flu vaccination recommended

Diabetes: important comorbidity; ulcers and wounds can be particularly morbid; foot care essential; treatment should follow guidelines for diabetes care

Exercise: supervised exercise program recommended; treadmill training increases 6-minute walk distance and walking time; 2012 trial showed greater improvements in treadmill walking time with supervised exercise compared with stent revascularization; better patient-reported quality of life with revascularization

Medical therapies for claudication: statins improve walking times; cilostazol (phosphodiesterase inhibitor) improves walking distance; should not be used in presence of HF; pentoxifylline no longer recommended; endovascular repair or surgery only for those with insufficient response and significant disability; endovascular repair with balloon angioplasty and stenting has lower perioperative risk; high success rates, low restenosis rates; aortoiliac stenting has better results than infrainguinal revascularization

Limb ischemia: *acute* — ABI <0.4, flat pulse waveforms, or absence of pedal arterial flow by Doppler; treat with urgent revascularization; *acute* — rare; caused by acute thrombosis of arterial flow; high morbidity and mortality; emergency — risk of amputation; 6 Ps: pain, paresthesias, pallor, pulselessness, paralysis and poikilothermia; use anticoagulation; angiography to locate obstruction; catheter-directed thrombolytics or revascularization; monitor for compartment syndrome

Suggested Reading

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Coronary Artery Disease

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Pathogenesis: coronary artery disease (CAD) results from buildup of atherosclerotic plaque; *atherosclerotic plaque* — complex entity composed of various constituents; lipids are important part of plaque progression; one reason cholesterol reduction with statins proven so effective; inflammatory cell component important part of plaque; inflammation an essential part of atherosclerosis; precipitates unstable coronary syndromes

Frequency: coronary atherosclerosis highly prevalent; one of most common diagnoses in aging population in US; growing in prevalence in parts of the world where previously less common — *eg*, China, India; important source of morbidity and mortality

Manifestations: vary among individuals or over an individual's lifetime; silent, asymptomatic coronary artery disease; stable angina (*ie*, chest discomfort) or equivalent symptoms occurring with physical activity or other precipitants (*eg*, emotional stress); unstable angina or equivalent symptoms occurring at rest or in accelerating pattern; non–ST-segment–elevation myocardial infarction (NSTEMI; older term: nontransmural MI); ST-segment–elevation MI (STEMI; older terms: Q-wave MI, transmural MI)

Stable vs unstable CAD: key differentiator — rupture of plaque resulting in thrombus formation; leads to ischemic syndromes; plaque erosion recently identified as potential cause of acute coronary syndromes (ACS) such as NSTEMI; learning more about manifestations of CAD

Risk factors: hypercholesterolemia, particularly elevation of LDL cholesterol; smoking; diabetes; hypertension; male sex often described as nonmodifiable risk factor (however, in recent decades, determined that CAD underappreciated in women); age; in general, at given age, risk higher in men than in women; after menopause, age/sex gap narrows; obesity sometimes classified as risk factor (some contend most effects of obesity occur through other risk factors — *eg*, diabetes, hypertension, hypercholesterolemia); may be independent component of obesity beyond effects on those risk factors; lack of exercise and unhealthy diet potential risk factors; some consider stress potential risk factor; inflammation, particularly arterial inflammation, possible risk factor, converting stable into unstable CAD

Symptoms: chest pressure — classic symptom of stable angina, typically occurring with defined level of physical activity; if symptoms rapidly worsen or occur at rest, considered unstable angina; transfer to emergency department; may be difficult to differentiate typical vs atypical symptoms

Atypical symptoms: many manifestations of coronary ischemia; dyspnea upon exertion; easy fatigability with physical activity; neck, arm, or back pain with physical activity; abdominal discomfort with physical activity

Demographics: atypical symptoms may occur more frequently in women than in men, older vs younger patients, patients with diabetes; however, in real-life setting, cannot really determine based on demographic factors; anyone with symptoms suggestive of ischemia warrants further evaluation in emergency department (*eg*, biomarkers, electrocardiogram [ECG], dynamic changes)

Workup: important to determine whether symptoms are stable or unstable CAD; if seems unstable, an expedited workup often initiated or facilitated through emergency department; recommended; if stable, workup can be conducted on outpatient basis

Physical exam: perform physical exam first; ascertain signs of heart failure (HF) (*eg*, rales over lung fields, S3 or S4 heart sounds on auscultation); S4 on cardiac exam may suggest ischemia; S3 may suggest HF; evaluate for heart murmur — *eg*, aortic stenosis can cause symptoms resembling angina; assess for arrhythmia

Electrocardiogram: next step if evidence of active ischemia (*eg*, new or dynamic ST depression); ST elevation may signify STEMI; T-wave inversion, less specific sign of active ischemia — if new or dynamic may represent ischemia; these ECG changes represent unstable angina; baseline ECG also useful for determining prior MI (*eg*, silent MI if prior Q-waves); evaluate for other abnormalities (*eg*, bundle branch block)

Exercise stress test: good screening test; next step if normal ECG, no major symptoms or signs on physical exam, patient capable of exercise, but suspicion of stable angina; exercise ECG will note ST-segment shifts that occur with exercise; if certain ST-segment shifts (*eg*, ST depression with exercise, especially if downsloping) suspect CAD; good first screening test; also demonstrates patient's functional capacity, length of time exercising before showing symptoms, and hypotension; presence of hypotension with exercise concerning — could be marker of severe CAD such as 3-vessel CAD or left main CAD, in which main artery to left side of heart has significant narrowing

Chemical stress test: if patient suspected of having CAD but incapable of exercise; appropriate only for stable CAD; adenosine/sestamibi stress test or dobutamine echocardiogram; not as useful as exercise stress test — cannot gauge functional capacity

Additional tests: imaging; nuclear studies or echocardiogram can be performed in conjunction with

exercise stress test if needed; necessary with chemical stress test; transthoracic echocardiogram useful to evaluate or detect murmurs, valvular heart disease, HF due to left ventricular (LV) dysfunction, pericardial diseases, prior MI and its extent, and for determining causes of chest discomfort other than CAD

Coronary artery calcium scores: used for gauging cardiovascular risk; controversial; in appropriate patients, can refine or reclassify risk assessment depending on patient's *Framingham Risk Score* — way of using risk factors to calculate projected risk of cardiovascular disease; for asymptomatic patients with intermediate Framingham Risk Score, coronary artery calcium score may be useful to reclassify risk; controversial because of cost and, to some degree, radiation exposure; useful in patients reluctant to start statin treatment, to provide further guidance about whether such therapy is truly indicated and beneficial; absence of coronary artery calcium means absence of CAD; should not be used to deter patient from following heart-healthy lifestyle; should not be used to avoid further testing in symptomatic patients

Computed tomography (CT) angiography: noninvasive coronary angiography; some controversy; can provide good resolution of proximal coronary arteries, though distal coronary arteries not always as well visualized; tachycardia or arrhythmia may produce gating issues and images may not be of good diagnostic quality; in those cases, beta blockers can be administered to lower heart rate; can be as useful as stress testing in terms of risk prognostication — however, stress testing more established and thus more common in initial evaluation of suspected CAD

Cardiac magnetic resonance imaging (MRI): limited role; can be excellent test for evaluation of myocardial or pericardial diseases; may also provide insight into valvular heart diseases, patterns of LV dysfunction, and differentiating between ischemic and other causes; because of expense and more limited availability, not a first-line test

Invasive diagnostic angiography (cardiac catheterization): very common test; safe but invasive with some degree of radiation exposure; often appropriate in patients with stable angina, abnormal stress test with significant ischemia, and persistent or worsening symptoms despite optimal medical therapy; can be used to determine extent of CAD

Ominous findings: left main CAD; 3-vessel CAD — involves left anterior descending artery, left circumflex artery, and right coronary artery; particularly concerning if in proximal vessels; treated with coronary artery bypass grafting (CABG); more recently, second-generation drug-eluting stents used successfully in patients with left main CAD; also patients with complex CAD, 3-vessel disease with lesions involving bifurcations with chronic total occlusions, and with high *syntax score* — risk score for assessing burden of angiographic CAD; if patient has diabetes, often better to treat with CABG than with stenting, assuming good candidate for CABG have few comorbidities, not high stroke risk; patients should be optimized on medical therapy first — *ie*, goal is to optimize medical therapy in stable patients and reserve coronary angiography for patients with ongoing symptoms and/or high-risk stress tests

Risks: some degree of complications, *eg*, bleeding from accessing an artery; typically uses femoral or radial artery (radial becoming more common); also risk with need for contrast exposure — can precipitate renal dysfunction in a patient with baseline renal insufficiency

Acute Coronary Syndromes

ACS differentiation: ST-segment elevation present on ECG, diagnose STEMI; if not present but other ECG abnormalities or positive cardiac biomarker (*eg*, troponin), diagnose NSTEMI; if negative biomarkers (at least initially) with ECG changes (*eg*, ST depression), diagnose unstable angina; if biomarkers negative and ECG does not clearly show abnormalities, can still be unstable angina — although not always ECG changes in unstable angina, diagnosis more definitive if dynamic ECG changes present; left circumflex artery can sometimes be electrocardiographically silent — *ie*, can be occluded and may not manifest as classic STEMI — some proportion of NSTEMIs are actually left circumflex artery occlusions

STEMI: important to characterize STEMI; requires prompt catheterization; time matters; "door-to-balloon time" is important — shorter is better; if catheterization lab unavailable, promptly administer thrombolytic or fibrinolytic therapy; approximately 90% to 95% treated with stents

NSTEMI: often involves invasive evaluation (*ie*, cardiac catheterization); depending on coronary anatomy, may be followed by stenting or CABG; approximately 60% of NSTEMI treated with stents; roughly 10% to 15% treated with CABG; remainder treated medically

Unstable angina: diagnosis has become less frequent with use of highly sensitive troponin assays; coronary lesion on angiography with true unstable angina

Routine stress testing: not recommended for asymptomatic post-ACS patients not entering cardiac rehabilitation; role of stress testing and ACS — lower-risk patients with no need for catheterization, or who decline catheterization; once patient treated or revascularized and asymptomatic, routine stress testing no longer recommended; if patient starting cardiac rehabilitation, stress test should be performed upon entry

Medical therapy: all patients with CAD likely require at least single antiplatelet therapy (*eg*, aspirin); all patients with CAD, barring allergy or contraindication, likely should receive statin to lower cholesterol; beyond that, treat patients with chest discomfort, including those with stable angina, with medical therapy such as nitrates and beta blockers; such therapies can also be useful for the treatment of chest pain in ACS; in cases of ACS, second antiplatelet agent (*eg*, clopidogrel or, more recently, more potent prasugrel and ticagrelor) often added (dual antiplatelet therapy), but higher bleeding risk and cost; in select patients with ACS, antiarrhythmics (*eg*, amiodarone, lidocaine) may be called for; revascularization would be best therapy, but until that can be accomplished, antiarrhythmics may be used; patients with ACS often also treated with intravenous anticoagulant (*eg*, unfractionated heparin or injectable low-molecular-weight heparin, such as enoxaparin)

Causes of ACS: in addition to plaque rupture and plaque erosion (lesser role for revascularization with plaque erosion), causes include, among others:

Coronary artery spasm (Prinzmetal angina) — best treated with nitrates and calcium channel blockers (eg, amlodipine, nifedipine); combination of long-acting calcium channel blockers and long-acting nitrates often useful

Coronary artery dissection, in which artery "unravels" — more common in certain situations: postpartum women; fibromuscular dysplasia; manifestations of connective tissue disorders (*eg*, Ehlers-Danlos syndrome)

Substance abuse — abuse of such substances as cocaine can precipitate plaque rupture or coronary spasm or result in other causes of chest pain

Chronic CAD: either in patients with stable angina after initial evaluation and treatment phase or patients with ACS once stabilized and in long-term care phase; routine stress testing or routine anatomic testing (*ie*, coronary CT angiogram or invasive angiogram) not recommended; clinical practice guidelines also do not recommend routine use of ECG monitoring in asymptomatic patients after stenting or CABG; cardiac rehabilitation important part of treatment, especially after revascularization; need appropriate diet, exercise regimen, weight loss, and stress reduction; smoking cessation important

Long-term medical therapy: medical therapy more commonly determined by cardiologist; if stable CAD, typically 1 antiplatelet medication, usually aspirin; if patient had ACS in past year, dual antiplatelet therapy recommended; aspirin and clopidogrel common in patients with stents, also prasugrel or ticagrelor with aspirin; important to reduce risk of recurrent ischemic events as well as prevent stent thrombosis;

Statins: in addition to antiplatelet therapy, statins should be part of long-term care; often recommended to use higher-intensity statins — refer to cholesterol guidelines for specifics; especially for ACS patients, often recommended to prescribe high-intensity statin such as atorvastatin 80 mg; many patients experience side effects with statins; in some cases, side effects due to nocebo effect, in which side effect is perceived even if receiving placebo; switching statins or lowering dose can help, even with nocebo effect; preventive cardiology clinic or lipid clinic can be useful in such cases;

Symptom control: also important with medical therapy; angina symptoms can be treated with beta blockers, calcium channel blockers, and nitrates; if no effect, try ranolazine

Special cases: atrial fibrillation or such situations as large anterior wall MI, in which an aneurysm has formed, or dyskinetic myocardium may warrant oral anticoagulants; much controversy about combining antiplatelets and anticoagulants — cardiologist should manage

Follow-up: important that patients with CAD have regular follow-up by PCP and/or cardiologist; reassess angina burden at every visit; also reassess adherence to medical therapy and lifestyle modification at every follow-up visit

Suggested Reading

Amsterdam EA et al: 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;64(24):e139-228; **Evidence Review Committee Members et al:** Duration of Dual Antiplatelet Therapy: a systematic review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2016;134(10):e156-78; **Levine GN et al:** 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*. 2016;134(10):e123-55; **Moscarelli M et al:** Surgical revascularisation of the acute coronary artery syndrome. *Expert Rev Cardiovasc Ther*. 2014;12(3):393-402.

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Heart Failure

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Background

Heart failure (HF): "congestive HF" no longer used; many heart disease patients who are not congested also have heart failure (HF)

Prevalence: HF increasing in prevalence and incidence; currently affects >4.5 million patients in the US; 0.5 million new cases annually; leading diagnosis for Diagnosis-Related Groups (DRGs) in patients aged >65 yr in all US hospitals; patients diagnosed in 1990s had 50% mortality rate within 5 yr of diagnosis

Importance: high cost; high morbidity, including hospitalizations; high readmission rate

Reasons for prevalence: many people have had bypass surgery; age of US population increasing, therefore more new cases of HF; better recognition and treatment for acute heart disease, including myocardial infarction (MI); however, does not address root of HF — ongoing ventricular syndrome

Pathogenesis: abnormal left ventricular (LV) function decreases cardiac output, resulting in stimulation of compensatory mechanisms; sympathetic nervous system releases epinephrine and norepinephrine, increasing heart rate and cardiac contractility; stimulation of renin-angiotensin system (RAS); ultimately, salt and water retention and abnormal vasoconstriction occur, causing impedance, or total peripheral resistance, to increase; LV functionality decreases further; vicious cycle; eventually leads to remodeling; unclear how quickly this will occur and varies among individuals

Remodeling: changes to myocardium in response to insult; distention, dilatation, and hypertrophy may occur; initially compensatory mechanism, but overcompensation leads to development of HF symptoms; early treatment of MI necessary to prevent remodeling

HFrEF (systolic dysfunction): HF with reduced ejection fraction; heart fibrils cannot shorten against increased load; often results from ischemic coronary disease — classic case is MI; patients may be asymptomatic

HFpEF (diastolic dysfunction): HF with preserved ejection fraction; group of multiple syndromes including hypertension, diabetes, obesity; ventricle cannot fill at normal pressures and thus pressure/volume curve shifts — small changes in volume ultimately become large changes in pressure; no good treatment guidelines

Causes: ischemic (coronary) disease or MI; longstanding hypertension; *cardiomyopathies* — may be idiopathic or familial; familial — estimated 20% of dilated cardiomyopathies; alcohol induced in certain patients; postpartum (commonly seen in women after first pregnancy) — more common in Black or hypertensive patients; some cardiomyopathies, if treated aggressively, can be reversed; viral myocarditis, *eg*, secondary to influenza; dilated cardiomyopathy can decompensate with secondary viral syndrome (*eg*, upper respiratory infection), but not vice versa

History: no substitute for complete and thorough medical history; chest pain or anginal symptoms; anginal symptoms may be atypical in women; hypertension; current recent use of cardiotoxic drugs — cardiomyopathy can occur with oncologic drugs, *eg*, doxorubicin (Adriamycin, Rubex) and trastuzumab (Herceptin); history of diuretic use; history of radiation therapy, especially in older patients — older radiation patterns extensive, could result in radiation carditis; exertion, exercise intolerance, changes in or lack of aerobic activity; orthopnea can give information about ventricular filling pressures; paroxysmal nocturnal dyspnea; obstructive sleep apnea — common in HF; discuss sleeping patterns with partner; discuss current or recent nonsteroidal anti-inflammatory drug (NSAID) use — could interfere with medications such as angiotensin-converting enzyme (ACE) inhibitors and can worsen any ongoing volume retention and renal dysfunction

Physical examination: assess volume status and cardiac output; dyspnea and exertion will provide a sense that volume may be elevated; jugular venous distention and jugular venous pressure assessment excellent for evaluating volume status; auscult lungs for rales; 90% of decompensated patients with HF may have clear lungs; bilateral lower-limb edema — if edematous, how high does it go?; patients in right-sided failure can have leg edema into upper thighs or even abdominal wall (anasarca); auscult heart for murmurs; listen for S3 or S4 sounds, which provide information about intraventricular pressures; measure carotid and peripheral pulses; electrocardiogram (ECG) helpful

Biomarkers: becoming more commonly used; use during admission to hospital, primarily natriuretic peptide B family; can use regular B-type natriuretic peptide (BNP) or N-terminal pro–B-type natriuretic peptide (NT-proBNP); elevation gives information about intraventricular pressure; if does not decrease by ≥30% during admission, patient at risk for readmission and possibly for high mortality; normal biomarkers will help differentiate symptoms associated with primary lung disease

Acute Decompensated Heart Failure

Definition: sudden or gradual onset of signs or symptoms of HF that require an unplanned office visit, emergency department visit, or direct hospitalization, in which primary diagnosis is acute HF

Presentation: >75% of patients previously diagnosed with HF and are decompensated state; newly diagnosed heart failure ≤20%; small percentage advanced or end-stage heart failure; every decompensation has reason — critical that physician learn about decompensation process to treat appropriately and minimize future occurrence; *eg*, patients who decompensate because of dietary indiscretion usually repeat pattern

Symptoms: dyspnea most common; second most common fatigue/weakness/exercise intolerance; edema; abdominal swelling due to ascites; distended or tender liver; weight gain from fluid retention; inanition, lack of appetite, or early satiety

De novo patients/differential diagnosis: acute MI presenting with pulmonary edema; critical or severe aortic stenosis with new arrhythmia, commonly atrial fibrillation; important to evaluate acute patients — why here?; patient's history during last few days; comorbidities

Characteristics: majority have preserved blood pressure; hypotension less common; >75% of patients have systolic blood pressure of >120 mm Hg; peripheral vasoconstriction may be occurring — cool extremities and diminished pulses indicate high peripheral resistance state; *note* — not all decompensated HF patients have HFrEF; >40% at speaker's institution actually have HFpEF and may have presented repeatedly for same symptoms; not understood why intraventricular pressures already high before patient develops excessive volume and already congested without noticeable weight change from fluid

Comorbidities: especially common in people aged >65 yr; diabetes common; hypertension; chronic renal disease, arthritis or other rheumatologic conditions; chronic lung disease; often difficult to distinguish whether symptoms related to lungs or to heart with pulmonary comorbidity

Admission prognosis: in-hospital mortality currently may be as low as 5%; length of stay varies, but in general 4.5 to 6 days; readmission rates unacceptable — about 20%; Medicare imposes penalties for readmission rates above national average; mortality post discharge not ideal; each hospitalization admission increases mortality — need to understand why; new guidelines — important not to stop current HF medications upon hospitalization

Kidney function: often abnormal at admission; increased venous pressure in kidney bed is problem; administering vasodilator, with or without diuretic, may lower central venous pressure and improve renal sodium blood flow; vasodilator + diuretic; proBNP can be helpful here — now recommended in guidelines; patients with ongoing renal dysfunction may have potential for worse outcome; hypotensive patients and those with an elevated BUN also of concern

Worrisome patients: those with renal dysfunction generally have poorer outcomes; hypotensive patients; patients with elevated blood urea nitrogen (BUN)

Medications

Diuretics: most commonly used drugs in HF; given as bolus or constant rate infusion (CRI); do not administer same dose as patient currently taking, *ie*, increase current dose; CRIs and higher doses result in higher output; creatinine initially increases but decreases within 48 hours — so initial creatinine rise not marker for outcome; check potassium and creatinine daily while in hospital; CRI diuretics easier to control amount of volume removed

Vasodilators: intravenous (IV) nitroglycerin inexpensive and leaves system quickly, as does nitroprusside; arterial line may be useful, and sometimes required by hospital, for nitroprusside; nesiritide (Natrecor) approved for acute HF; demonstrated no difference in mortality and hospitalization in ASCEND-HF clinical trial, but can be given to patients with no response to nitroglycerin or nitroprusside; serelaxin and ularitide — newer vasodilators being studied; have not shown significant benefits in clinical trials

Inotropes: reserve inotropes for "wet and cool" patients — severely abnormal cardiac outputs not improving with vasodilator; inotropes not vasopressors — cause vasodilation more than vasoconstriction and may be beta agonists like dobutamine or dopamine; dopamine at low doses not vasoconstrictor; inotropes increase cardiac output; milrinone (Primacor) — phosphodiesterase inhibitor and inodilator because of vasodilating properties; milrinone in combination with another inotrope, *eg*, dobutamine, commonly used for patients awaiting heart transplantation; can combine milrinone with another vasodilator if adequate cardiac output or blood pressure

Disadvantages of inotropes: increased risk of myocardial oxygen consumption; tolerance; increased arrhythmias; higher mortality rates; avoid inotropes if possible; if need for inotrope, get HF or cardiology consult; when administering dobutamine or dopamine, discontinue or avoid beta blockers; beta blocker discontinuation unnecessary

Diagnostic tools:

Echocardiogram: allows for obtaining pressures, valve function, and even prognosis; guidelines recommend repeating when definitive change in clinical status

Nuclear scans: multigated acquisition scan (MUGA) and others; can provide more exact number for ejection fraction, although may be unnecessary

Magnetic resonance imaging (MRI): increasingly used; capable of diagnosing issues within myocardial muscle itself; *eg*, noncompaction cardiomyopathy demonstrates loose trabeculations within ventricle

Chronic Heart Failure

New York Heart Association (NYHA) Classification: subjective classification of HF; can help determine mortality risk; chart classification at each visit

NYHA Class I — no symptoms

NYHA Class II — no symptoms unless stressed in exercise or activity

NYHA Class III — symptoms apparent with less than normal activity

NYHA Class IV — difficulty speaking full sentence without taking breath

Neurohormonal cascade: RAS system and sympathetic nervous system (with epinephrine and norepinephrine); within RAS system, angiotensin II — vasoconstrictor; stimulates aldosterone and vasopressin release; sodium

retention and volume retention stimulated by these neurohormones; angiotensin II also "master remodeler" — stimulates collagen synthesis and increases fibrosis, so plays large role in cardiac remodeling; critically important that HFrEF patients be treated appropriately with RAS inhibition

Treatment:

Angiotensin-converting enzyme inhibitors (ACEis): CONSENSUS clinical trial — NYHA Class IV patients; evaluated enalapril (Epaned, Vasotec) vs placebo; trial finished early because drug showed significant benefits; drug approved for HF; Studies of Left Ventricular Dysfunction (SOLVD) clinical trial — NYHA Class II and III patients on enalapril vs placebo; demonstrated 16% decrease in 4-yr mortality when added to conventional therapy in patients with HFrEF

Angiotensin II receptor blockers (ARBs): block receptor instead of enzyme; several clinical trials studied valsartan (Diovan) and candesartan (Atacand); both approved for use as alternatives to ACE inhibitors for HF

Mineralocorticoid receptor antagonists: in US, spironolactone (Aldactone) primarily used; eplerenone (Inspra) used in Europe; highly efficacious in NYHA Class II-IV for HFrEF; TOPCAT trial encouraging for spironolactone use in HFpEF patients; recommended for use in combination with ARB or ACE inhibitor

Beta blockers: 3 beta blockers have demonstrated significant reductions in heart failure mortality of about 34%: carvedilol (Coreg), metoprolol succinate (Lopressor, Toprol-XL), and bisoprolol (Zebeta); current guidelines recommend switching patients on atenolol (Tenormin) to one of these drugs

Angiotensin receptor-neprilysin inhibitors (ARNi): sacubitril/valsartan (Entresto); PARADIGM-HF trial finished early because combination drug showed significant benefits; 20% reduction in cardiovascular death of HFrEF patients compared with enalapril 10 mg twice daily; also reduction in hospitalizations; approved for treatment of HFrEF and added to guidelines

Ivabradine (Corlanor, Procoralan): newer drug approved for use in patients who have heart rates >70 bpm despite beta blockade and for reduction in hospitalizations; not approved for mortality reduction

Side effects of RAS inhibitors (mineralocorticoid inhibitors and beta blockers): *hypotension* — via drug itself or excessive diuresis; always decrease diuretic dose by half when doubling RAS inhibitor, ARB, or ARNi; *renal function* — small rise in creatinine may be acceptable and small changes may decrease within 48 hours; hyperkalemia often accompanies increased creatinine; decreased potassium once achieved by administering sodium polystyrene sulfonate (Kalexate, Kayexalate, Kionex); newer drug, patiromer (Veltassa), now approved for treatment of hyperkalemia; important to also discuss potassium-containing foods with patients — *eg*, strawberries and avocados — very high in potassium

Exercise: critical; HF-ACTION trial determined exercise training for HFrEF patients was safe, improved quality of life, and showed modest improvements in combined endpoints of mortality and hospitalizations; Medicare now covers HFrEF patients who have been on adequate medical therapy for ≥6 weeks for cardiac rehabilitation; inactivity detrimental to patients

Transitions of care: Get With The Guidelines — Heart Failure from American Heart Association demonstrated postdischarge visits that occur 7 to 10 days after discharge can impact readmission rates; Medicare added performance measure for postdischarge visit, which should be scheduled before patient leaves hospital; medication reconciliation important; should include determining if the patient can obtain medications and if covered by insurance; some patients may have no insurance, so important for physician to find generic medications at manageable price; tracking patients via telemetry may be helpful, *eg*, phone calls and having patients chart their weight and call frequently with that information; implantable monitors or smartphone apps may be useful

Key Points

1. There is no substitute for a complete and thorough medical history.
2. A good physical examination in HF should concentrate on the volume and estimated cardiac output.
3. Every HF decompensation has an underlying cause, and it is the physician's responsibility to determine the decompensation process.
4. Many medications are available for HF therapy. These have been tested and been proven in a large number of patients to be effective. Medications will not work if they are not prescribed or administered.

Suggested Reading

American Heart Association: Guidelines and statements. www.myamericanheart.org. Published 2013. Updated 2017. Accessed May 22, 2018; **American Heart Association:** Rise above heart failure. www.heart.org. Updated 2016-2017. Accessed May 22, 2018; **European Society of Cardiology:** Guidelines. www.escardio.org. Accessed May 22, 2018; **Heart Failure Society of America:** www.HFSA.org. Accessed May 22, 2018.

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Valvular and Structural Heart Diseases

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Aortic stenosis: most common symptomatic valvular heart disease in US adults; history and physical exam paramount; causes obstruction to left ventricle (LV) outflow tract, eventually leading to left ventricular hypertrophy (LVH); can cause symptoms such as angina, dyspnea, and syncope; presence of any of these symptoms in appropriate patient warrant further evaluation with transthoracic echocardiography

Signs and symptoms: characteristic systolic murmur, appreciated best over base of heart (aortic area); may also be signs of LVH, either on estimating heart size on physical exam, evidence of LVH on electrocardiogram, or enlargement on chest x-ray; valve area can be calculated based on echocardiography; in general, valve area <1.0 cm^2 is severe aortic stenosis — should prompt treatment consideration if symptomatic; no proven medical therapy; mechanical treatment includes surgery or, more recently, transcatheter aortic valve replacement (TAVR); pressure gradient across valve can be calculated; in general, mean pressure gradient >50 often corresponds to valve area <1.0 cm^2

Asymptomatic mild aortic stenosis: murmur may prompt echocardiogram; patients should have repeat echocardiography every 3 to 5 years; symptoms should be assessed more frequently to make sure no rapid progression of symptoms — unusual with mild degree of stenosis, especially in absence of dramatic symptoms

Causes: most common cause: calcification occurring with age; rheumatic causes — infrequent in US, but should be considered in individuals from regions with more prevalent rheumatic heart disease; bicuspid aortic valves can cause aortic stenosis and aortic regurgitation; often some pathology in ascending aorta (aortopathy) immediately adjacent, so can be aortic aneurysm; when bicuspid aortic valve causes aortic stenosis, tends to occur in younger patients than does calcific aortic stenosis

Asymptomatic severe aortic stenosis: patients with preserved LV function (normal ejection fraction on echocardiography) can be managed with close clinical follow-up; echocardiography every 6 to 12 months; need aortic valve replacement (AVR) not needed at that point, but close follow-up necessary and patient must be reliable; if any change in symptomatology, echocardiogram should be conducted; for impaired ventricular function, surgical AVR should be considered if patient is candidate — LV function will likely continue to deteriorate; can be tricky because LV function may be caused by some other pathology and severe aortic stenosis coexistent or partially contributory; tests such as dobutamine echocardiogram to see if LV perks up at all, to see if better flow across aortic valve; need to be done in cardiology practices or in specialized heart clinics; asymptomatic patients with bicuspid aortic valve should undergo transthoracic echocardiography yearly if aortic root or ascending aortic diameter >4 cm, to monitor potential for aneurysm; higher in those patients — usually bicuspid aortic valve has some degree of aortopathy, even if subclinical

Symptomatic aortic stenosis: start with good history and physical, characterization of murmur, echocardiography; valve area <1.0 cm^2 consistent with severe aortic stenosis, along with consistent symptoms, usually reason to consider either surgical aortic AVR or TAVR; invasive coronary angiography (cardiac catheterization) often performed as part of workup to view coronary anatomy; if severe triple-vessel disease and tight valve, and if patient is surgical candidate, likely to have AVR and coronary artery bypass grafting (CABG); former gold standard — crossing valve with wire and then catheter to measure gradient; not typically done now if echocardiogram is diagnostic and symptoms consistent with aortic stenosis; if echocardiographic measurements ambiguous or if issues with echocardiographic images, that type of direct measurement may have value in catheterization lab; to avoid small risk of embolization, including small risk of stroke, generally not crossing tight, calcified aortic valves unless clinical reason to measure gradient that way; coronary arteries still typically evaluated invasively to determine presence of concomitant coronary artery disease (CAD)

Treatment: past — aortic balloon valvuloplasty worked well acutely, occasionally acute aortic regurgitation occurred that caused problems for patients; with more conservative balloon valvuloplasty (smaller balloons), acute aortic regurgitation became less frequent; acute results included reasonable improvements in valve area that give patient symptomatic relief; problem was restenosis — aortic valve would again become stenotic and symptoms would recur; for patients who are candidates for surgical procedures, gold standard was — and, in many cases, is — surgical AVR (mechanical or bioprosthetic valves); patients already on anticoagulation therapy (*eg*, because of atrial fibrillation [AFib]) often receive mechanical valve; for younger patients (*eg*, 50 years) not on anticoagulants, mechanical valve historically would be recommended — durable as long as anticoagulation is taken; for older patients (*eg*, 75 years), bioprosthesis would be inserted so not necessary

to receive lifelong anticoagulation therapy (unless patient has AFib); various factors go into selection of mechanical vs bioprosthetic valve; requires discussion between surgeon and the patient

TAVR: more minimally invasive, often percutaneous approach (*ie*, femoral arterial access); less frequent approaches include direct apical access (LV apex accessed surgically) or surgical or percutaneous access of other arteries (*eg*, subclavian artery) for minimally invasive valve replacement

Use in types of surgical candidates: strong data for TAVR in patients who are not surgical candidates — PARTNER trial showed reduction in mortality with TAVR vs best medical therapy; in those patients (assuming surgical candidate) with few comorbidities, appropriate to perform AVR — TAVR recommended; for patients at high (but not prohibitive) surgical risk, TAVR at least as good as conventional surgery; shorter recovery times; in general, in patients with high or prohibitive surgical risk, TAVR current standard of care; in patients with intermediate surgical risk, TAVR also used; results appear to be as good as surgery; 5-year data suggest TAVR valves durable; randomized clinical trials are ongoing in patients with low surgical risk to determine if TAVR as good as surgery but less invasive; TAVR may become predominant way to treat symptomatic aortic stenosis across range of surgical risk; for now, patients at low surgical risk and some at intermediate surgical risk who are good candidates should have surgery; if concomitant complex CAD, CABG may be performed as well; in patients at high surgical risk with tight proximal right coronary artery lesion, TAVR plus stent to right coronary artery typically done

Medical treatment: aortic stenosis is mechanical problem, so not much in the way of medical therapy; statins can be useful in patients with aortic stenosis — many people with aortic stenosis also have concomitant CAD and often dyslipidemia; can be difficult to increase cardiac output, especially if patient has really critical aortic stenosis (*eg*, valve area of 0.7 cm^2 or 0.5 cm^2); should be careful about things that quickly drop preload; always worry about giving sublingual nitroglycerin to nitrate-naive patients with critical aortic stenosis, especially if standing — drop their preload; cardiac output could drop, and they could syncopize; be cautious about quick, aggressive blood-pressure lowering

Aortic regurgitation: leakage of blood across aortic valve; results in diastolic murmur — often harder to hear than systolic murmurs; having patient lean forward can help auscultate aortic regurgitation; having patient lean forward on end expiration helps bring out murmur slightly more; if aortic regurgitation suspected based on exam, echocardiogram is next step; patients with asymptomatic mild aortic regurgitation typically require echocardiography every 3 to 5 years; should monitor symptoms during that time — rapid progression of symptoms may prompt echocardiogram sooner; asymptomatic patients with moderate aortic regurgitation should be evaluated clinically each year and have echocardiography every 1 to 2 years, but generally medical or surgical intervention not needed other than good general medical care, blood pressure control, etc

Causes: dilation of aortic root; sometimes occurs in patients with bicuspid aortic valves; also can be seen in Marfan syndrome; other connective tissue disorders (*eg*, ankylosing spondylitis) can be associated with aortic root dilation and sometimes aortic regurgitation; although infrequent, syphilis can cause aortitis that may present years after original infection, and can be associated with aortic dilation and regurgitation; endocarditis (infection the valve) uncommon in US, but rheumatic fever can cause many valvular problems, including stenosis and regurgitation

Management: can be more challenging to manage than aortic stenosis, less algorithmic; symptomatic patients with severe aortic regurgitation on echocardiography should have surgical AVR

TAVR: has been used for aortic regurgitation, but limited experience; if aorta dilated (often dilated with aortic regurgitation), valve may not seat well; TAVR has been performed in some cases; in patients without obvious symptoms but who seem to have severe aortic regurgitation, exercise stress test can help determine if exercise provokes symptoms; LV function important in asymptomatic patients with aortic regurgitation; serially falling ejection fraction can be an indication for surgery before LV decompensates; address before that happens so patient does not develop heart failure (HF); assess LV dimensions and examine end systolic and end diastolic diameters; if increasing, can indicate surgery or more frequent clinical evaluations and echocardiographic evaluations; cutoffs vary for these values (consult various guidelines, *eg*, American Heart Association/American College of Cardiology guidelines for valvular heart disease)

Surgical AVR: indicated if patient symptomatic, LV starting to decompensate in terms of ejection fraction, or LV enlarging; many patients may also need replacement of part of ascending aorta if dilated; as with aortic stenosis, aortic regurgitation patients who will undergo surgery typically have cardiac catheterization (invasive coronary angiography) to determine if coronary artery disease exists that also needs surgical treatment at same time as AVR; in the past, usually would do aortogram to assess for aortic regurgitation in catheterization lab; typically not done now unless echocardiogram is ambiguous; as with all valvular heart disease after surgery, patients should be followed closely over time to make sure they do not develop recurrent problems with valve; all patients need to be counseled about risks for endocarditis — in particular, if aortic pathology (*ie*, aneurysm that needs to be followed closely and serially over time, including with imaging)

Mitral valve disease: *mitral regurgitation* produces a systolic murmur; *mitral stenosis* produces a diastolic murmur; these murmurs often best heard over apex

Mitral stenosis often results from rheumatic heart disease (in US, other than in communities with lots of recent immigrants from certain parts of the world, not a lot of rheumatic mitral stenosis — if in community with many immigrants from areas with high prevalence of rheumatic fever, be on lookout for it); mitral stenosis easy to just miss if checked in a noisy room; with significant mitral stenosis, AFib often present, so that can sometimes be clue during physical exam;

pregnancy can sometimes provoke previously asymptomatic mitral stenosis to become symptomatic

Treatment: treatment of severe and symptomatic mitral stenosis can be surgical (if highly calcified valve); often, if anatomy is right, balloon valvuloplasty can yield excellent results, assuming different echocardiographic risk scores show mitral valve suitable for valvuloplasty; prior to any surgical valve replacement, coronary angiography performed to determine concomitant CAD and need for bypass surgery

Mitral regurgitation: many different causes, including ischemia and prior infection (*eg*, endocarditis); in older people, calcification can form on mitral annulus; in younger patients, mitral valve prolapse; rheumatic fever, though uncommon in the US; dilation of LV, such as from HF; usually, patients have AFib; in general, mitral stenosis graded as severe when valve area <1 cm^2, and often gradient across valve >10 mm Hg; moderate mitral valve stenosis tends to be in range of 1 cm^2 to 1.5 cm^2; *transthoracic echocardiography* — excellent test to assess mitral valve area and mitral gradients; *transesophageal echocardiography* (TEE) provides even crisper pictures for mitral stenosis, mitral regurgitation, or suspected mitral valve endocarditis; if transthoracic echocardiogram not definitive, TEE can be quite useful; — minimally invasive; can be done with conscious sedation, but be sure patient has no esophageal strictures or other contraindications; safe test with high yield — clear pictures and ability to precisely define gradients and degrees of regurgitation and presence or absence of vegetation; ejection fraction often normal or supranormal early on; low ejection fraction with mitral regurgitation means ejection fraction very low; in mitral regurgitation, some of blood goes in wrong direction — even if "normal" ejection fraction, not all forward ejection fraction; decrement in ejection fraction in mitral regurgitation is warning sign of decompensating LV;

Treatment: if mitral valve prolapse, can sometimes be repaired without need for valve replacement; younger patients with mitral stenosis and AFib frequently get mechanical valve; if symptoms consistent with severe mitral regurgitation (*eg*, bad dyspnea) and echocardiogram shows severe regurgitation, surgery usually resolves symptoms; need to take care in terms of timing; in general, with valvular heart disease, better to address before LV starts to exhibit deterioration — bad for patient (symptoms) and surgery becomes higher risk as ejection fraction drops; in mitral vs aortic position, mechanical valves tend to have higher risk of thromboembolism if patient not appropriately anticoagulated — partly because of higher risk of AFib, and even more important for mechanical mitral valve that anticoagulation be uninterrupted; sometimes mechanical mitral valves have higher targets for anticoagulation — in part, depends on type of valve itself; important to be familiar with what valve patient has; surgeon and managing cardiologist will provide guidance

Percutaneous approaches: starting to come into clinical practice; device called *MitraClip* (based on figure-of-8 stitch) — clips leaflets of mitral valve together to reduce degree of regurgitation; EVEREST trials have shown this technique not quite as good as surgery, but potential option in patients who are not surgical candidates; whether applicable for every form of mitral regurgitation is matter for study; *technique* — enter femoral vein, transseptal puncture from right atrium into left atrium, then place clips across mitral valve leaflets, trying to reduce regurgitant volume; attempts being made to place percutaneous valves in mitral position, as done successfully with TAVR for aortic position; mitral valve much larger, geometry more variable, and difficult to fixate valve, but TAVR valves have been placed in mitral position for failed mitral bioprostheses and native valves in cases of heavy calcification; results to date have been good, but some patients do not do well; sometimes TAVR valve placed in mitral position can impinge on LV outflow tract and create small obstruction; in near future, especially with developments in technology, might have percutaneous mitral valves that produce good, durable results

Tricuspid valve regurgitation: can be challenging to treat, especially if severe; often leads to hepatic congestion, making patients poor surgical candidates; newer percutaneous approaches seem promising, especially because surgical approaches less than optimal

Structural Heart Diseases

Ventricular hypertrophy: several different forms of hypertrophy; *concentric hypertrophy* — perhaps best known; can occur with pressure overload from aortic stenosis or many years of untreated or poorly treated hypertension; valvular heart disease can contribute to *eccentric hypertrophy*

Asymmetric septal hypertrophy: sometimes seen in hypertrophic obstructive cardiomyopathy (HOCM), which can produce systolic murmur; can sound somewhat like aortic stenosis; various maneuvers can sometimes help differentiate HOCM murmur from an aortic stenosis murmur; distinction often made on echocardiography; both conditions can coexist — aortic stenosis with asymmetric septal hypertrophy from hypertension manifesting that way instead of more concentric pattern; physical exam can be useful to help find cause of that patient's dyspnea, or other symptoms possibly caused by both aortic stenosis and HOCM (*eg*, syncope); echocardiographic finding in HOCM is *systolic anterior motion (SAM)* of mitral leaflet — anterior leaflet gets sucked in and abuts area of septal hypertrophy, resulting in *dynamic outflow obstruction* — can cause symptoms of HOCM; volume dependent; dehydration can make it worse; maneuvers that lead to less preload can also make maneuver worse; explains how different maneuvers like Valsalva or squatting, or squatting and standing up — that can change preload conditions — can affect and exacerbate murmur; easier to understand pathophysiology than to memorize what maneuvers cause what changes in murmurs

Atrial septal defects and patent foramen ovale: patent foramen ovale (PFO) present in about 25% of people; atrial septal defects slightly more uncommon, especially in adults

PFO: indication for PFO closure or for antiplatelet therapy in asymptomatic patients; some suggestive data pointing pointed to role for PFO closure to reduce

migraines, but those data are weak; migraine currently not indication for PFO closure; no support for closing PFOs routinely in patients at potential risk for stroke; in patients with *cryptogenic stroke* (all other causes of stroke have been evaluated and ruled out), PFO closure reduces risk of recurrent stroke — based on recent data; slightly higher risk of AFib periprocedurally from device closure; relatively safe procedure involving femoral vein approach, crossing PFO, and placing clamshell-like closure device; shown to be effective compared with antiplatelet therapy in patients with cryptogenic stroke; has not been compared against non-vitamin K oral anticoagulants

Atrial septal defects: patients with small atrial septal defects (pulmonary-to-systemic blood-flow ratios or Qp/Qs <1.5 to 1) with no associated symptoms and no right heart enlargement can be followed clinically; when atrial septal aneurysm identified incidentally, no further evaluation, medical treatment, or intervention needed; PFO in conjunction with atrial septal aneurysm in someone with cryptogenic stroke predicts higher rate of a recurrent stroke and might be indication for PFO closure

Ventricular septal defects: small membranous ventricular septal defects without left heart enlargement, pulmonary hypertension, recurrent endocarditis, or valve regurgitation; can be observed clinically

Endocarditis: infectious (more common) or noninfectious causes (sometimes called sterile or marantic endocarditis [eg, from lupus]); infection usually reason for diagnosing endocarditis; intravenous (IV) drug users at higher risk — sometimes more predisposing to right-sided endocarditis, though even left-sided endocarditis does occur from systemic spread; person with damaged valve who has bacteremia may develop endocarditis; conventional wisdom has been risk of endocarditis exists after dental procedures; may be recall bias rather than true association or may be associated with more significant dental procedures; link between prior dental procedures and endocarditis not viewed as strongly now, but may be associated with more significant dental procedures

Evaluation: careful history and physical exam, auscultation, listening for murmurs, examination for other stigmata of endocarditis (*eg*, splinter hemorrhages on nails); blood cultures key to diagnosing endocarditis; echocardiography is important, but if highly suspicious, TEE should be pursued if transthoracic not revealing; suspect endocarditis in patient with prosthetic heart valve and fever or otherwise seem unwell; threshold for obtaining blood cultures should be very low — once prosthetic valve becomes infected, difficult to clear infection with antibiotics; repeat surgery can be challenging, especially if sewing ring on which valve is seated develops infection; try to avoid if at all possible

Treatment: in general, prolonged IV antibiotics; often involves placement of peripheral IV line, PICC line, and home antibiotic therapy for ~6 weeks; repeat blood cultures to ensure the infection cleared; if complications, surgery may be required; severe regurgitation from endocarditis, embolic complications (*eg*, stroke or embolization to other critical organs), heart block from erosion into conduction system (may happen with aortic valve abscesses or aortic valve endocarditis), or HF, must consider surgery if patient is candidate; try to get IV antibiotics on board to try to clear infection; timing of surgery can be challenging if patient has complications of endocarditis; surgeon does not want to sew in while bacteremia exists or while active local infection at site of valve — prosthetic valve likely to get seeded; if patient has had stroke, do not want to wait until next stroke occurs, but need to get some degree of infection control with antibiotics before operating; careful discussion among cardiologist, cardiac surgeon, and infectious disease specialist needed

Antibiotic prophylaxis: not recommended for nondental procedures, including TEE and genitourinary or gastrointestinal procedures in absence of active infection; should be limited to those with prosthetic cardiac valve, history of infective endocarditis, unrepaired cyanotic congenital heart disease, repaired congenital heart defects with prosthesis or shunt, or residual defect, or valvulopathy following cardiac transplantation; important to keep in mind current indications for infective endocarditis

Pericardial disease: various potential pericardial diseases; pericardial effusions can occur; most extreme form can lead to *tamponade* — drop in cardiac output because of effusion; tamponade is emergency; true tamponade manifests with hypotension; can progress very rapidly; treatment for tamponade generally pericardiocentesis, often placing pericardiocentesis needle in subxiphoid position and draining it; if patient about to code, perform at bedside, often aiming for left shoulder; if possible, better with echocardiographic guidance, even better with both echocardiographic and fluoroscopic guidance in catheterization laboratory; some people attach ECG leads to check for injury if one goes too far and hits ventricle instead of being in pericardial space; echo-guided pericardiocentesis is optimal approach to minimize complications; fluoroscopy can also be useful adjunct; using both probably easiest way to tap pericardial effusion

Causes: malignancy (common cause in hospitals with cancer centers); trauma can cause pericardial effusion; if aortic dissection suspected (potential cause of pericardial effusion and tamponade), indication for surgery; patient needs to go to operating room (OR); performing pericardiocentesis can backfire — pericardial effusion could be tamponading; relieving it could exacerbate situation and result in more bleeding in pericardial space and lead patient to decompensate; role for OR if pericardial effusion cannot be drained percutaneously; usually can deal with tamponade percutaneously; if effusion keeps recurring, surgical pericardial window often required; other causes of pericardial effusions include viral infections, idiopathic, and tuberculosis (infrequent in US today, but earlier often caused pericardial calcification)

Pericarditis: inflammation of pericardium; may occur after cardiac surgery; may be caused by viral infection; may be idiopathic; sometimes can lead to effusion, but most often no significant effusion or tamponade; patients with acute pericarditis but no high-risk features (*eg*, fever, leukocytosis, acute trauma, abnormal cardiac markers, immunocompromised, oral anticoagulant use, large concomitant pericardial effusions, evidence of cardiac tamponade) can be managed medically, usually outpatient, with close clinical follow-up

Suggested Reading

Adler Y et al: 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2015;36(42):2921-64; **Nishimura RA et al:** 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Thorac Cardiovasc Surg*. 2014;148(1):e1-132; **Otto CM et al:** Updated 2017 European and American guidelines for prosthesis type and implantation mode in severe aortic stenosis. *Heart*. 2018;104(9):710-3; **Yusuf SW et al:** Pericardial disease: a clinical review. *Expert Rev Cardiovasc Ther*. 2016;14(4):525-39.

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Cardiac Arrhythmias

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Overview of conduction system: heartbeat initiated in sinoatrial (SA) node in right atrium near junction with superior vena cava; electrical pacemaker signal transmitted through the atrium to atrioventricular (AV) node near the medial tricuspid annulus; AV node slows conduction and blocks high rate transmission, eg, in atrial fibrillation and atrial flutter; electrical impulse traverses common His bundle and divides into right and left bundle branches at apex of interventricular septum; right bundle branch conducts the impulse to right ventricular tissue, arborizing into Purkinje Fibers, which activate contraction of cardiomyocytes; left bundle divides into anterior and posterior fascicles, then into Purkinje fibers which stimulate contraction of cardiomyocytes of left ventricle; resting heart rate normally 60-100 beat per minute (bpm) and is modified up or down by sympathetic and parasympathetic nervous systems and circulating catecholamines; intrinsic heart rate in denervated heart (as in heart transplant) averages 100 bpm; maximum predicted heart rate during peak exercise is 220 minus age in years

Pathology: may occur anywhere along conduction system pathways and/or in atrial and ventricular free muscle; arrhythmias/dysrhythmias may be divided into abnormally fast rhythms/tachyarrhythmias and abnormally slow rhythms/bradyarrhythmias; are also tachy-brady arrhythmias; further divided into supraventricular and ventricular arrhythmias

Supraventricular Arrhythmias

Definition: arrhythmias rising in atria, AV node, or His bundle

Premature atrial complexes (PACs): ectopic beats arising from foci in atria; common, increase with age; when infrequent and asymptomatic — benign except as indicators of potential atrial pathology, eg, atrial enlargement, hypertrophy, inflammation, fibrosis, or infiltrative diseases; when frequent and symptomatic may require antiarrhythmic therapy with beta blocker or non-dihydropyridine calcium channel blocker; may trigger sustained supraventricular tachyarrhthmias

Supraventricular tachycardia (SVT): reentry using an accessory pathway; supraventricular arrhythmias with atrial and/or ventricular rates >100 bpm; include inappropriate sinus tachycardia, atrial tachycardia, junctional tachycardia, AV node reentrant tachycardia (AVNRT); various forms of atrial-ventricular tachycardia (AVRT) mediated by accessory pathways between atria and ventricles; SVT if abrupt in onset and offset called paroyxysmal SVT (PSVT); prevalence 2-3/1000 population, incidence 36/100,000/year; female/male risk 2:1; risk of PSVT increases >5x after age 65; those referred for ablation are usually younger adults with low frequency of other cardiovascular diseases; have equal sex distribution

AVNRT/AVRT: equal ratio in adolescent patients; AVNRT becomes dominant with aging; accessory pathway is basis for both AVRT and AVNRT; AVNRT associated with dual pathways involving AV node, one of which is abnormal; AVRTs involve connections variably remote from AV node and spanning AV groove connecting atrium and ventricle; pathways are congenital, abnormal strands of electrical conducting tissue; in AVRT a manifest accessory pathway conducts antegrade from atrium to ventricle, causes a ventricular pre-excitation pattern on resting ECG typical of Wolff-Parkinson-White (WPW) syndrome; antidromic AVRT is SVT or atrial fibrillation (AF) conducting down an accessory pathway and retrograde back through the AV node, causing a wide complex tachycardia; orthodromic AVRT has narrow QRS complex conducting antegrade through AV node, retrograde through the pathway; type has implications for prognosis and treatment

Mechanisms: atrial tachycardia may be focal, ectopic, multifocal (MAT), or macroscopic reentrant tachycardia, eg, with sinoatrial node reentrant tachycardias; in inappropriate sinus tachycardia (IST), P wave is similar to sinus P wave, but rates are inappropriate for degree of activity (>100 bpm at rest or averaging >90 bpm/24 h and not due to another cause

Clinical presentation: majority of PSVT patients present with symptomatic palpitations, tachycardias, shortness of breath, lightheadedness, fatigue, less commonly with chest discomfort or syncope; panic disorder may be mistakenly diagnosed; pre-excitation on resting ECG, rapid conduction of antidromic SVT, and/or antidromic AF with rapid rates and short refractory period can cause sudden cardiac death, demands therapeutic intervention

Diagnosis: resting 12-lead ECG during tachycardia may provide definitive diagnosis; ECG taken during irregular ventricular rhythm suggests atrial fibrillation, atrial flutter, or multifocal atrial tachycardia; regular SVT may represent AVNRT or AVRT or atrial or junctional tachycardia (origin in AV node or His bundle with 1:1 conduction); location, timing, and morphology of P wave help to distinguish among these; in AVNRT, the P wave is within or at the end of the QRS complex and is narrow and negative in inferior leads; in orthodromic AVRT, there is a longer delay between the QRS and retrograde P wave and P wave may be distinct from the QRS, with

an R-P interval >90 milliseconds (ms); in both, the QRS-P is shorter than the P-QRS and they are designated short RP tachycardias; atrial tachycardias have a long R-P interval where the ectopic P wave precedes the QRS

Diagnostic/monitoring modalities: diagnosis can be made using 24– to 72-h Holter monitor, a longer-term external event monitor (up to 30 days), or implantable cardiac monitor (up to 3 years); the induction of SVT in an electrophysiologic study is a helpful and relatively safe invasive diagnostic test in difficult cases and can be coupled with ablation procedure in appropriate cases

Treatment: strength of recommendations to be discussed follows American College of Cardiology (ACC) and American Heart Association (AHA); Class 1 represents strong recommendations ("is recommended/useful"); Class 2a represents moderately strong recommendations ("is/can be useful"); Class 2b represents weak recommendations ("may be reasonable/useful"); Class 3 represents no benefit or actual harm ("is not recommended/indicated"); vagal maneuver for regular narrow complex SVT of unknown origin, junctional tachycardia, known AVNRT or orthodromic AVRT without pre-excitation on resting ECG is Class 1; for SVT presenting to a competent medical facility, IV adenosine is Class 1; synchronized cardioversion reserved for acute treatment of hemodynamically unstable SVT when vagal maneuvers and pharmacologic therapy are ineffective or unfeasible; if vagal maneuvers and adenosine are ineffective, IV beta blockers, diltiazem, or verapamil can be used acutely for hemodynamically stable SVT, with synchronized cardioversion for failed or infeasible cases; giving these medications orally in stable patients may be reasonable if other options not available; promising future option for outpatients with acute PSVT is intranasal agents, which are rapidly absorbed and fast acting, eg, verapamil analog itripamil; for acute management of pre-excited AF or AVRT in hemodynamically unstable patients, synchronized cardioversion is recommended; IV ibutilide or IV procainamide are recommended in stable patients; for preexcited atrial fibrillation, digoxin, amiodarone, beta blockers, diltiazem, verapamil are potentially harmful, as they block AV node and may facilitate conduction down the accessory pathway; for acute management of suspected focal atrial tachycardia, IV beta blockers, diltiazem, or verapamil useful for stable patients and synchronized cardioversion for unstable patients; IV adenosine can be useful and IV amiodarone or ibutilide may be reasonable to diagnose tachycardia mechanism and potentially restore sinus rhythm; for ongoing management of suspected focal atrial tachycardia, catheter ablation is recommended for symptomatic patients; oral beta blockers, diltiazem, verapamil, flecainide and propafenone and potentially sotalol or amiodarone are reasonable pharmacologic options; for patients with symptomatic or asymptomatic preexcitation, exercise testing in sinus rhythm that results in loss of preexcitation and loss during ambulatory monitoring is useful to identify patients at low risk for rapid conduction over accessory pathway; electrophysiologic (EP) testing is reasonable for risk stratification in these patients, particularly when preexcitation is persistent; catheter ablation is reasonable in these patients if EP testing identifies high-risk substrate for an arrhythmic event, ie, short refractory period <240 ms; however, observation is also reasonable option; an EP study is a Class 1 recommendation for risk-stratification of symptomatic patients with preexcitation to assess for possibility of life-threatening arrhythmic events; for acute treatment of multifocal atrial tachycardia, IV metoprolol or verapamil can be useful, with oral verapamil, diltiazem, or metoprolol for ongoing management; important to identify and treat underlying and inciting pathophysiologic factors such as pulmonary disease; ivabradine is reasonable for ongoing management of patients with IST without a reversible cause, and beta blockers may be considered alone or in combination with ivabradine

Atrial fibrillation (AF) and atrial flutter: irregular supraventricular tachyarrhythmias; often co-present, overlap with each other in same patient

Atrial fibrillation: most common sustained cardiac arrhythmia; irregular RR intervals and rapid and regularly undulating atrial activity; ~5 million Americans affected; prevalence expected to increase to >12 million by 2050; preferentially affects older individuals (>70 yrs); lifetime risk of AF 1 in 4 adults; associated with increased thromboembolic risk and is major cause of stroke — accounts for 15% of strokes in US; increases stroke risk fivefold and is associated with more severe strokes; increases risk in asymptomatic and symptomatic patients

Classification: valvular or non-valvular; rheumatic mitral stenosis is prime example of valvular AF; hypertension, aging, obesity, diabetes, cardiometabolic syndrome, obstructive sleep apnea, systolic and diastolic heart failure, ischemic heart disease, hyperthyroidism, and systemic inflammatory conditions are associated with increased risk of non-valvular AF; familial AF (many genetic patterns) presents at younger age

Etiologies: automatic foci, most frequently in pulmonary veins as they enter left atrium — mechanism dominant in paroxysmal AF; focal rotors within the atrium with outward fibrillatory conduction are another mechanism for sustained AF; multiple atrial wavelets and local autonomic nerve stimulation additional proposed mechanisms; evidence of atrial inflammation and fibrosis are found on pathological studies, and degree of fibrosis corresponds to duration of AF

Clinical presentation: palpitations, tachycardias, lightheadedness, fatigue, dyspnea, or, less commonly, syncope; in the presence of pre-excitation or WPW, AF can present as cardiac arrest; older individuals with slowed AV nodal transmission may be asymptomatic; clinical evaluation requires careful history, physical examination, ECG, chest x-ray, echocardiogram, blood chemistries, thyroid function tests, stress test if coronary disease suspected, possibly pulmonary function tests

Three categories ("3 Ps"): paroxysmal AF — AF terminating spontaneously or with intervention within a week; persistent AF — continuous AF for over 7 days; long-standing persistent AF — continuous AF >1 year, previously called permanent AF, now indicates that a decision has been made to leave patient in AF and not pursue attempts to restore sinus rhythm, as improved methods have restored sinus rhythm in many cases of long-term AF

Treatment: for ventricular rate control in acute setting, IV administration of a beta blocker or non-dihydropyridine calcium channel antagonist recommended in non-pre-excited AF,; IV amiodarone is reasonable for critically ill patients without pre-excitation in whom rate control is inadequate; in pre-excited AF, digoxin, amiodarone, beta blockers, diltiazem, and verapamil are potentially harmful as they block the AV node; electrocardioversion is recommended acute treatment of hemodynamically unstable AF; for AF durations >48 h or of uncertain duration, ≥3 wks of anticoagulation before cardioversion recommended; alternatively, screening for an atrial thrombus by transesophageal echocardiography (TEE) at the time of cardioversion is reasonable; long-term treatment goals include rate control, rhythm control, and stroke prevention

Rate control: goal is resting ventricular rate <80 bpm; target rate <110 in asymptomatic patients with preserved left ventricular function; with increasingly rapid average rates during sustained persistent AF, risk of tachycardia-related cardiomyopathy with heart failure increases; beta blockers or non-dihydropyridine calcium channel blockers recommended for chronic rate control, with digitalis or digoxin reserved for heart failure or as a second drug as needed; amiodarone, part of management for rhythm control, should be used for rate control only as last resort; catheter ablation of AV node with prior or simultaneous placement of pacemaker controls rate but leads to dependence on continuous ventricular pacing, associated with contractile dyssynchrony or pacing-mediated cardiomyopathy; AV node ablation with pacing considered only when pharmacologic therapy cannot achieve rate control and when primary ablation of AF is not a consideration; stroke volume is maximized and rate controlled when sinus rhythm is restored and maintained, especially important for physically active individuals and those with symptomatic AF and rapid rate despite medication

Rhythm control: cardioversion recommended for patients with AF or atrial flutter to restore sinus rhythm; IV ibutilide. a Vaughan-Williams Class III drug, is useful pharmacological cardioversion option for stable AF of short duration; oral dofetilide, flecainide, and propafenone also are indicated for pharmacological cardioversion; for cardioversion of patients not on chronic anticoagulation and with duration of atrial fibrillation or flutter known to be <48 h, IV heparin, low molecular weight heparin, or direct oral anticoagulant should be given before or immediately after cardioversion, followed by ≥4 wks of oral anticoagulation for low thromboembolic risk patients and long-term for high thromboembolic risk patients; recommended pharmacologic therapy to chronically maintain normal sinus rhythm includes sodium channel blockers flecainide and propafenone (class Ic), potassium channel blockers (class III) drugs, specifically amiodarone, sotalol, dofetilide, and dronedarone; flecainide and propafenone may be preferred initially for AF in the absence of ischemic or other structural heart disease and amiodarone and other class III drugs in presence of structural disease, eg, heart failure or coronary disease; due to their pro-arrhythmic risk, dofetilide and sotalol should be started during in-hospital observation; because of its potential long-term toxicity, amiodarone should be used only when other appropriate agents have failed or are contraindicated

Catheter ablation: often uses radio frequency; can restore and maintain sinus rhythm with AF, but has some risk of complications, rarely. death; has class 1 recommendation for symptomatic paroxysmal AF after failure of at least one class I or class III drug; has class 2a recommendation as first-line therapy for paroxysmal and persistent AF; can be considered for treatment of longstanding persistent AF after at least one failed antiarrhythmic drug trial; in recent CABANA study, ablation as first-line therapy for AF in patients with increased stroke risk was shown to have greater efficacy for rhythm control than pharmacologic therapy and trended, but did not reach significance, in reducing composite endpoint of death, disabling stroke, serious bleeding, and cardiac arrest; patients <75 y benefitted most from ablation, while those >75 y did better with initial pharmacologic treatment; most common approach to catheter ablation includes isolation of the origins of the four pulmonary veins; usual technique is with radiofrequency burns, but thermal cooling can also be used; additional linear or circular lines can be added for persistent and refractory cases; AF ablation can be done at the time of surgery performed for other reasons, such as valve replacement or coronary bypass

Thromboembolic stroke prevention: thrombus in AF usually originates in stagnant blood pooling in left atrial appendage; embolizes to brain or elsewhere at time of conversion back to sinus rhythm or during ongoing AF

CHA_2DS_2-VASc score: factors in addition to AF that impact thromboembolic risk include age, hypertension, heart failure, cardiovascular disease, diabetes, female gender, and prior thromboembolic event (stroke, transient ischemic attack [TIA] or peripheral thromboembolism); factors incorporated into risk score called CHA_2DS_2-VASc; a score of 2 is given for age >75 and prior stroke; other factors earn a score of 1; with a score of 0, risk is low and antithrombotic therapy may be omitted; with a score of 1, use of aspirin, anticoagulant, or no antithrombotic therapy reasonable; if only positive factor is female sex, net benefit of anticoagulant treatment is unlikely; with score of ≥2, oral anticoagulants recommended

Anticoagulation: in patients for whom anticoagulation is indicated, warfarin or a non-vitamin K antagonist oral anticoagulant (NAOAC), also called direct oral anticoagulant (DOAC) is recommended; dabigatran is a factor II inhibitor; rivaroxaban, apixaban, and edoxaban are factor X inhibitors; non-pharmacologic stroke prevention options include isolation or removal of the left atrial appendage, which may be catheter-based (Watchman device)or performed surgically at the time of other open-heart procedures; DOACs cause less intracranial bleeding than warfarin, do not require ongoing prothrombin time monitoring, can be given in fixed doses with more rapid onset and offset kinetics, and are more effective than aspirin with an acceptable incremental bleeding risk over aspirin; antidotes to DOACs have been developed for emergent reversal; DOACS have higher costs than warfarin, and although they have similar or superior overall efficacy in non-valvular AF, their efficacy is lower than warfarin for

patients with mechanical valves, for which they are contraindicated

Recommendations specific to individual patient groups with AF: anticoagulation of patients with hypertrophic cardiomyopathy regardless of CHADS-VASc score; use of beta blocker to control ventricular rate in patients with thyrotoxicosis; a non-dihydropyridine calcium channel blocker to control rate with AF in chronic obstructive pulmonary disease (COPD) patients; immediate cardioversion in hemodynamically compromised pre-excited AF patients; IV digoxin or amiodarone for acute control of heart rate in non-pre excited patients with overt heart failure; in cardiac or thoracic surgery, beta blocker recommended for post-operative AF, non-dihydropyridine calcium channel blocker when beta blocker is inadequate; preoperative amiodarone considered reasonable as prophylactic therapy for patients at risk of post-operative AF

Atrial flutter: macro reentrant supraventricular tachyarrhythmia; the most common reentrant pathway propagates counterclockwise around the tricuspid annulus and proceeds superiorly along atrial septum then inferiorly along right atrial wall and through isthmus between inferior vena cava and tricuspid valve annulus; produces a sawtooth like atrial pattern on the ECG, predominantly negative in leads II, III, and aVF, and has late positive deflection in V1; atrial rate is ~300 bpm; in reverse atypical flutter, reentrant pathway propagates in clockwise direction, and direction of atrial activation pattern on ECG is reversed; atypical non-cavotricuspid isthmus-dependent atrial flutters use other macroreentrant circuits, such as around the mitral valve annulus, around an atrial scar, for example, one that has resulted from a healed surgical incision or ablation line

Association with AF: often occurs in same clinical settings as AF; atrial flutter 1/10 as common as AF; flutter can cause or be caused by AF; after cavotricuspid isthmus ablation of atrial flutter, 20% to 50% of patients develop AF within 1-3 years; patients with prior AF, increased left atrial size and left ventricular dysfunction, or other structural or ischemic heart disease are at increased risk of subsequent AF; atrial flutter may develop in AF patients treated with flecainide, propafenone, or amiodarone, which slow conduction but have less effect on refractoriness; atrial flutter is associated with increased thromboembolic stroke risk and anticoagulation indications are the same as for AF

Diagnosis: symptoms of atrial flutter with rapid ventricular conduction are like those of other SVTs and include palpitations, lightheadedness, fatigue, dyspnea, and syncope; on ECG, atrial flutter may have 2:1 conduction at a rate of 150 bpm or variable conduction, eg, alternating 2:1 with 3:1 or 4:1; former must be differentiated from other forms of SVT; IV adenosine increases AV block to reveal underlying atrial flutter waves; latter must be distinguished from AF

Acute treatment: similar to AF; synchronized cardioversion recommended for hemodynamically unstable atrial flutter and elective synchronized cardioversions for stable patients; pharmacologic cardioversion with IV ibutilide or oral dofetilide and with IV or oral beta blockers, diltiazem, or verapamil; the latter is also used for acute rate control in stable patients; with atrial pacing wires, rapid atrial pacing is useful to achieve cardioversion; IV amiodarone can be useful for acute rate control in systolic heart failure when beta blockers are contraindicated or ineffective; acute antithrombotic recommendations same as those for AF; for ongoing management, catheter ablation of cavotricuspid isthmus is effective and safe; class 1 indication in symptomatic patients as first-line therapy or after failed pharmacologic trials; catheter ablation also indicated in patients with recurrent symptomatic atrial flutter after failed pharmacologic therapy; catheter ablation in patients with asymptomatic recurrent atrial flutter has weak recommendation; beta blockers, diltiazem, or verapamil are useful to control rate in hemodynamically tolerated atrial flutter, although their efficacy in this setting is less than that with AF; amiodarone, dofetilide, and sotalol can be used to maintain sinus rhythm; ongoing management with antithrombotic therapy and atrial flutter aligns with recommended antithrombotic therapy for AF

Ventricular Arrythmias

Definition: arrhythmias occuring below AV node or His bundle and in ventricles; mechanisms of ventricular arrhythmias include abnormal automaticity, triggered activity induced by early or late afterdepolarizations, and reentry; substrate for ventricular arrhythmias includes myocardial ischemia, hypertrophy, fibrosis or scarring, and infiltrating substances causing ion channel dysfunction and abnormal cell-to-cell signal transmission and conduction

Premature ventricular complexes (PVCs): found on 12-lead ECGs in <1% of general population <20 y, increasing to 2.7% at >50 y:; on 24-hour ambulatory monitor, about 50% of subjects may have PVCs; frequent PVCs (>30/h or >1000 per day) are associated with increased cardiovascular risk and mortality; more useful as prognostic markers to look for underlying structural heart disease than as target for treatment; when highly symptomatic or frequent (>15% of beats), may cause a PVC-induced cardiomyopathy, treated with catheter ablation or antiarrhythmic therapy with a beta blocker or amiodarone; for symptomatic PVCs in normal heart, use a beta blocker or a non-dihydropyridine calcium channel blocker indicated to suppress PVCs and reduce symptoms; if these are ineffective or not tolerated, an antiarrhythmic medication can be considered

Sustained ventricular arrhythmias: >100 bpm lasting >30 seconds or requiring earlier termination due to hemodynamic compromise; include ventricular tachycardia (VT) and ventricular fibrillation (VF); frequently symptomatic and cause palpitations, pre-syncope, syncope, or even cardiac arrest; portend a high mortality risk especially if associated with structural or ischemic heart disease; require evaluation and treatment; in contrast, unsustained VT is ≥3 beats that terminate spontaneously within 30 seconds; VT may be monomorphic (one QRS form) or polymorphic (with changing forms); a specific form of VT called torsades de pointes is a polymorphic VT in the setting of a prolonged QT interval; VF characterized by rapid, irregular electrical activity at ventricular rate >300 bpm; leads to cardiac arrest unless rapidly terminated

Sudden cardiac death: unexpected death occurring within an hour of symptom onset or death occurring within 24 h of an asymptomatic state and presumed to be related to a cardiac arrhythmia or other hemodynamic catastrophe

Diagnosis: patients presenting with syncope in whom a ventricular arrhythmic cause is documented or thought to be likely should be hospitalized for evaluation, monitoring, and initiation of treatment; 12-lead ECG should be obtained for diagnosis during ongoing hemodynamically stable tachyarrhythmias; if patient with suspected ventricular arrhythmia is in sinus rhythm, ECG should be analyzed for evidence of cardiac structural or conduction system disease; exercise treadmill testing is diagnostically useful in patients with symptoms of arrhythmia on exertion; ambulatory ECG monitoring is useful to evaluate whether symptoms suggestive of arrhythmia are associated with arrhythmia; implanted cardiac monitors ca be used in patients with infrequent symptoms suspicious of ventricular arrhythmias; echocardiography can be used in patients with high risk ventricular arrhythmia to evaluate cardiac structure and function; magnetic resonance imaging (MRI) or computed tomography (CT) can be useful to further characterize structural heart disease; cardiac MRI with late gadolinium enhancement is useful to diagnose myocardial infiltrative disease and assess sudden cardiac death risk in patients with suspected non-ischemic cardiomyopathy; measurement of B-type natriuretic peptide or NT-pro-BNP is useful for prognosis for sudden cardiac death or cardiac arrest in the presence of structural heart disease; in younger adults with non-ischemic cardiomyopathy or conduction disease in the setting of a positive family history, consider genetic testing; after sudden cardiac arrest, coronary CT angiography or invasive angiography is recommended to assess extent of coronary artery disease and need for revascularization; in patients with functional heart disease and syncope or other symptoms suggestive of ventricular arrhythmia, an electrophysiologic study can be useful to assess risk of sustained arrhythmia and need for implantable cardioverter-defibrillator (ICD)

Prevention: for pharmacological prevention of sudden cardiac death, patients with heart failure and reduced ejection fraction (≤40%), treatment with beta blocker, mineralocorticoid receptor antagonist, and an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or ARB-neprilysin inhibitor is indicated

Treatment: revascularization recommended for patients with sustained ventricular arrhythmias and survivors of sudden cardiac arrest who have ischemic heart disease or anomalous origin of a coronary artery suspected to be causal; treatment with a beta blocker is reasonable in patients with symptomatic non-life-threatening ventricular arrhythmia

Acute management of specific ventricular arrhythmias: cardiopulmonary resuscitation (CPR) per protocol for cardiac arrest; treat unstable ventricular arrhythmias with direct current cardioversion — if these persist or recur, IV amiodarone is indicated; consider patients with wide complex tachycardia of unclear type to have VT unless demonstrated otherwise; patients with polymorphic VT or VF with ST elevation myocardial infarction (MI) should undergo emergency revascularization; IV beta blockers can be useful in patients with polymorphic VT; synchronized cardioversion is preferred acute treatment in patients with sustained monomorphic VT and structural heart disease; IV procainamide can be used to terminate stable VT with cardioversion applied for drug failure; emergently applied catheter ablation reserved for cases recurrent or refractory after cardioversions; in patients without structural heart disease but with ECG morphologies of specific VT types, verapamil can be useful for a verapamil-sensitive type VT; beta blockers can be useful for outflow track VT with cardioversion recommended for drug refractory cases; for subsequent therapy, catheter ablation is recommended while verapamil or beta blockers can be useful in drug responsive non-ablation candidates

Secondary prevention of sudden cardiac death: for secondary prevention in patients with ischemic heart disease and history of cardiac arrest due to VT/VF or who experience hemodynamically unstable VT not due to reversible cause, ICD is indicated; in patients with non-ischemic cardiomyopathy, ICD indicated in survivors of sudden cardiac arrest due to VT/VF or who experience hemodynamically unstable VT or stable VT not due to reversible cause; ICD also recommended in patients with ischemic heart disease who experience unexplained syncope and who have inducible, sustained monomorphic VT on EP study; in non-ischemic cardiomyopathy patients who experience syncope presumed to be due to ventricular arrhythmia, an ICD or EP study to guide risk stratification is reasonable; if an ICD is not an option, amiodarone may be considered

Primary prevention of sudden cardiac death: for patients with ischemic heart disease who are in New York Heart Association (NYHA) classes 2 or 3 on guideline-directed medical therapy and who have LVEF of ≤35% or those in NYHA class 1 with an EF of ≤30% and who are at least 40 days post-MI and/or at least 90 days post-revascularization, an ICD is recommended; those with non-sustained VT due to prior MI, an EF of ***≤40%***, and inducible VT or VF on EP study, ICD is recommended; for outpatients in NYHA class 4 and are candidates for transplantation or an LV assist device, an ICD is reasonable; in patients with non-ischemic cardiomyopathy despite optimal medical therapy, and are in NYHA class 2 or 3 with symptoms and EF ≤35% despite optimal medical therapy an ICD is recommended; ICD may be considered in NYHA class 1; more liberal guidelines apply to those with malignant Lamin A/C mutation-associated cardiomyopathy, and the decision to implant an ICD is dependent on the expectation of at least 1 y of meaningful survival; ICD provides high value and cost-effectiveness in primary prevention of sudden cardiac arrest and intermediate value and cost-effectiveness for secondary prevention if risk of sudden cardiac death considered high and the risk of non-arrhythmic death to be low

Recurrent ventricular arrhythmia: amiodarone or sotalol are useful to suppress recurrent ventricular arrhythmia in ischemic heart disease and non-ischemic cardiomyopathy with recurrent sustained ventricular arrhythmia with significant symptoms; catheter ablation for prior MI or non-ischemic cardiomyopathy and recurrent ventricular arrhythmia, ICD shocks and ongoing beta blocker therapy; in patients with prior MI or nonischemic cardiomyopathy and recurrent ventricular arrhythmia who have failed on antiarrhythmic drug medication, catheter ablation is recommended or can be useful

Congenital long QT syndrome: in symptomatic patients (eg, syncope or cardiac arrest) with a QTC >470 ms, beta blocker is recommended; if beta blocker ineffective

or not tolerated, ICD or cardiac sympathectomy is recommended; genetic counselling and testing recommended to guide therapy and assess at-risk relatives

Catecholaminergic polymorphic ventricular tachycardia: beta blocker is indicated — if ineffective, flecainide, cardiac sympathectomy or ICD recommended; genetic counseling and testing are reasonable

Brugada syndrome: an ICD is recommended in patients with type 1 Brugada ECG pattern and history of sudden cardiac arrest, sustained ventricular arrhythmia, or syncope likely due to ventricular arrhythmia; for recurrent ICD shocks or non-ICD candidates, quinidine or catheter ablation recommended

Medication-induced ventricular arrhythmias: give digoxin antibodies to patients with sustained ventricular arrhythmia due to digoxin toxicity; give IV magnesium to patients with torsade de pointes ventricular arrhythmia associated with acquired QT prolongation and bradyarrhythmia at baseline; replace potassium to 4 mmol/L; for refractory torsade de pointes, increasing heart rate with pacing or isoproterenol recommended

Special considerations: patients with arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, cardiac sarcoidosis, or neuromuscular disorders in addition to cardiac arrhythmias in structurally normal hearts will not be discussed but should be kept in mind

Bradycardias and Conduction System Disorders

Basis: dysfunction of sinus node-adjacent atrial tissue, AV node, bundle of His, and/or the bundle branches are the basis of bradycardias and conduction system disorders; changes in cellular function such as degenerative fibrosis and other age- and disease-related processes are responsible for intrinsic conduction system disorders and explain increased incidence in older adults, beginning in seventh decade of life; in contrast, vagally mediated bradyarrhythmias are more common in younger individuals, including well-conditioned athletes; infectious agents, such as Lyme carditis, are rare but potentially reversible causes of bradyarrhythmias and heart block; common bradycardias and conduction system disorders include sinus node dysfunction, chronotropic incompetence, AV nodal and infranodal block, and bundle branch block

Sinus node dysfunction: sinus rate of <50 bpm and/or sinus pause of ≥3 seconds; ranges from chronic slow heart rates to episodic sinus node arrest with pauses or combination of the two

Chronotropic incompetence: failure to achieve 80% of expected maximum heart rate — 220 minus age at maximum exercise capacity

Conduction block: AV, infranodal, bundle branch block

Second degree Mobitz type 1 (Wenckebach) block: occurs in AV node; represented by P waves at constant rate <100 bpm with progressively increasing PR intervals followed by a single non-conducted P wave

Mobitz type 2 block: more distal, unstable block; constant PR intervals before and after dropped beat; with 2:1 AV block, every other P wave is blocked whether progression has occurred by way of a type 1 or 2 Mobitz mechanism; cannot be discerned with certainty from ECG; narrow QRS often present with type 1 and a wide QRS with type 2

Third degree or complete heart block: no evidence of AV conduction despite atrial rate greater than the junctional or ventricular escape rate

Location of block: may be AV nodal or infranodal or may occur in the right bundle or in one or both components of left bundle (left anterior and left posterior fascicles

Clinical presentation: present across broad spectrum of manifestations from asymptomatic or minimally impactful on energy and functional capacity to lightheadedness or presyncope to frank syncope, depending on degree and duration of conduction system dysfunction and any cardiac comorbidities; sudden death is a rare risk

Clinical evaluation: careful history and physical examination; 12-lead ECG to determine rate, rhythm, and conduction status and evidence for associated structural heart disease; exercise ECG testing is reasonable to evaluate suspected chronotropic incompetence or exertion-related bradyarrhythmias; ambulatory electrocardiography useful to correlate rate and rhythm with symptoms, with the particular type and duration of monitoring based on nature and frequency of symptoms; implantable cardiac monitor is reasonable for undiagnosed and infrequent symptoms with >30-day intervals; correlation between symptoms and ECG findings is gold standard of diagnosis and forms basis for pacemaker and other treatments; EP study considered on very selective basis if non-invasive evaluation is non-diagnostic; echocardiography is recommended for disorders often associated with ischemic or structural heart disease, including left bundle branch block, Mobitz type 2 second-degree AV block, third degree block, and others that suggest structural disease; advanced imaging with transesophageal echocardiography, cardiac CT angiography, cardiac MRI, or nuclear imaging reasonable for more complete assessment of structural heart disease; laboratory tests reasonable to identify potential underlying causes, eg, thyroid function tests, potassium levels, lyme titers; genetic counseling and testing of first degree relatives of patients with a known causative mutation is recommended; testing for sleep apnea is recommended for patients with symptoms during sleep; sleep apnea should be treated if found

Treatment of sinus node dysfunction: most cases do not require acute treatment; with hemodynamic compromise, atropine is reasonable, with a catecholamine as second-line option; if bradycardia is associated with medications, eg, beta blockers, calcium channel blockers, or digoxin, use of specific reversal agents is reasonable; use of aminophylline or theophylline is reasonable for post-heart transplant sinus bradycardia and with sinus node dysfunction after spinal cord injury

Pacing: temporary transvenous pacing for medication-refractory unstable patients is reasonable; reversible causes should be addressed before considering permanent pacing; permanent pacing indicated in symptomatic patients with symptoms attributable to sinus node dysfunction; dual- or single-chamber atrial pacing recommended over single-chamber ventricular pacing; there is no lowest heart rate or set duration of a sinus pause to indicate pacing; decision should rely on a correlation with symptoms in individual patients; dual chamber pacemakers are programmed to minimize ventricular pacing; single-chamber ventricular

pacing reasonable in situations when frequent ventricular pacing is not expected; permanent pacing indicated in those with sinus bradycardia associated with necessary medical therapy, eg, beta or calcium channel blocker therapy; in symptomatic patients with chronotropic insufficiency, permanent pacing with rate-responsive programming is reasonable to increase exercise-related heart rates; long-term medical therapy for sinus node dysfunction is not generally efficacious; oral theophylline may be considered in lieu of or to predict effects of permanent pacing

Treatment of heart block: acute management of bradycardias due to AV block related to transient or reversible causes (eg, drug toxicity, infectious or inflammatory conditions) should first have cause-directed medical care with supportive cardiac care, including temporary IV pacing if necessary; proceed directly to permanent pacing for symptomatic second or third degree AV block in those on chronic necessary medications (eg, beta blockers, antiarrhythmics)and those with AV block secondary to cardiac sarcoidosis; atropine is reasonable for symptomatic patients with second or third degree AV block at the AV nodal level, with a catecholamine as a second line agent if ischemic heart disease is unlikely; may consider treatment with IV aminophylline with inferior MI and bradyarrhythmias; temporary transvenous pacing reasonable in symptomatic patients with second or third degree block refractory to medical therapy; permanent pacing recommended in symptomatic patients with AV block without a reversible cause or without resolution despite therapy; for those with symptoms of unclear cause such as light-headedness or dizziness, who have first degree or Mobitz type 1 second degree AV block on ECG, additional monitoring should be considered to establish correlation between symptoms and dysrhythmia prior to considering permanent pacing; exercise testing reasonable for evaluation of symptoms during exercise

Specific indications for permanent pacing for chronic bradyarrhythmias: 1) acquired second degree Mobitz type 2 AV block, high grade AV block, or third degree AV block not due to reversible causes regardless of symptoms; 2) for infiltrative cardiomyopathy such as cardiac amyloidosis or sarcoidosis, reasonable to consider adding defibrillator capability; 3) in patients with neuromuscular diseases associated with conduction disorders such as myotonic dystrophy type 1 with the above conditions, or with HV interval >70 ms regardless of symptoms, or patients with Lamin A/C gene mutation, limb girdle, or Emery-Dreifuss muscular dystrophies and PR interval >240 ms, and in those with myotonic dystrophy type 1 with QRS >120 ms or fascicular block, reasonable to add defibrillator capability to pacing; 4) permanent AF and symptomatic bradycardia; 5) patients who develop symptomatic AV block as a result of guideline-indicated and necessary medical therapy

Additional considerations for pacing methods: upgrade to a dual chamber pacemaker recommended for patients in sinus rhythm who develop pacemaker syndrome of heart failure due to frequent single-chamber ventricular pacing; cardiac resynchronization therapy with biventricular or His bundle pacing is reasonable in those with mildly to moderately reduced ejection fraction (36%-50%) who require a substantial percentage of ventricular pacing (>40%)

Bundle branch or fascicular blocks: conduction disorders with 1:1 conduction; QRS duration ≥120 mms indicates complete right and left bundle branch block; a duration of 110-119 ms indicates incomplete bundle branch block or non-specific intraventricular conduction defect (IVCD); may sometimes produce symptoms on their own, but may be importantly prognostic; left bundle branch block may cause symptoms in heart failure by causing desynchronized ventricular contraction; conduction blocks indicate a higher risk of AV block and should prompt further diagnostic testing in presence of symptoms of bradycardia

Treatment of conduction disorders: in patients with syncope and bundle branch block, an HV interval of ≥70 ms or infranodal block on EP study, permanent pacing is recommended; pacing also is recommended in patients with alternating bundle branch block regardless of symptoms; in patients with heart failure and mildly to moderately reduced ejection fraction (36%-50%) and left bundle branch block with QRS of >150 ms, cardiac synchronization therapy may be considered

Special populations: placement of epicardial pacing wires reasonable during cardiac surgery — coronary artery bypass grafting and mitral valve replacement or repair; recommended routinely for aortic valve replacement or repair and tricuspid valve procedures; permanent pacing recommended prior to discharge for patients with symptomatic, non-resolving sinus node dysfunction or AV block after cardiac surgery; observation for bradyarrhythmia advised for patients after transcatheter aortic valve replacement who develop new bundle branch block; consider permanent pacemaker for persistent new left bundle branch block; patients with second degree Mobitz type 2 AV block, high grade AV block or third degree AV block persisting after alcohol septal ablation or surgical myectomy for hypertrophic cardiomyopathy should receive permanent pacing prior to discharge; in patients with acute MI, temporary pacing indicated for symptomatic bradycardia related to sinus node dysfunction or AV block; should wait to see whether block resolves before considering permanent pacing; permanent pacing indicated after observation period with second degree Mobitz type 2 AV block, high grade AV block, or third degree AV block; atropine reasonable for symptomatic patients with sinus bradycardia or AV block in setting of acute MI; in patients requiring permanent pacing and with or at risk for ventricular arrhythmias, need for defibrillator should be assessed prior to device implantation; shared decision-making with clinicians and patient and consideration of quality of life issues important whenever implantation of device is recommended

Suggested Reading

Agewall S et al: Coronary artery disease and arrhythmias. *Eur Heart J Cardiovasc Pharmacother* 2017 Apr 1;3(2):69-70; **Cecchin F et al:** Cardiac arrhythmias in adults with congenital heart disease: pacemakers, implantable cardiac defibrillators, and cardiac resynchronization therapy Devices. *Card Electrophysiol Clin* 2017 Jun;9(2):319-28; **Guasch E et al:** Diagnosis, pathophysiology, and management of exercise-induced arrhythmias. *Nat Rev Cardiol* 2017 Feb;14(2):88-101.

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Pulmonary Diseases

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Testing — case presentation: Ms Smith is a 52-year-old woman with a dry, non-productive cough that has been worsening for 6 months; denies shortness of breath (SOB), wheezing, fever, other constitutional symptoms; medical history includes mild hypertension; takes amlodipine; she had asthma as a child, but says that she grew out of it; does not have seasonal allergies; has not tried any respiratory medications to try to relieve her symptoms; reports no specific relieving or exacerbating features of her cough; used to smoke 1 pack of cigarettes daily from ages 16 to 40, but quit 12 years ago; has worked in a casino for the last 20 years and is exposed to secondhand smoke; sometimes works nights; her cough wakes her from sleep and is worse after work

Three main types of pulmonary tests: spirometry, lung volumes, DLCO (diffusing capacity for carbon monoxide)

Other useful tests: bronchial challenge testing, pulse oximetry, arterial blood gases (ABG), exercise testing, measurement of muscle forces

Spirometry: patient begins the test with tidal breathing, followed by a strong inhalation and a forced expiration; for optimal results, need calibrated equipment and an informed technician; portable office-based testing is increasingly available; tests may be inexpensive and easy; indications include most patients with respiratory complaints; important findings include the measurement of the forced expiratory volume in the first second (FEV_1), the ratio of the FEV_1 to the forced vital capacity (FVC), and the flow-volume loop; results will determine normal, obstructive lung disease, or restrictive lung disease; data are reported as the actual number obtained on the test and as the percentage predicted; we use 3 tests that must vary by less than 5%; we expect that a patient will have at least a 6-second exhalation for a quality test; the best of the 3 reproducible tests is in the final report

Limitations: if the testing is done between asthma exacerbations, the spirometry may be normal; not useful for general preoperative screening; screening should be done before surgical procedures only in patients with respiratory complaints

Implications: a ratio of FEV_1 to FVC <69% may be used to diagnose chronic obstructive pulmonary disease (COPD) in accordance with the GOLD (global guidelines for COPD) Guidelines; compare the patient's values with normal predicted values; a test is abnormal if the test result is >2 standard deviations outside the normal range

Patient results: our patient had normal spirometry

Bronchoprovocation/bronchial challenge testing: determines if a patient has bronchospasm; involves serial spirometric measures, each preceded by the administration of an agent known to provoke bronchospasm, usually methacholine; indications include patients suspected of having asthma or another type of bronchospastic disorder; candidates include patients suspected of asthma with normal spirometry, atypical symptoms of chronic cough, a suspicion of occupational asthma, or an occupation that demands screening for asthma; most useful when the prior predicted probability of asthma is about 50%; not useful if likelihood of asthma either low or high

Precautions: avoid patients with signs/symptoms of active bronchospasm; test should be used with caution in any patient with evidence of active obstruction on spirometry; laboratory must have qualified personnel, medications, and equipment to deal with bronchospasm

Procedure: obtain baseline spirometry; many laboratories will use nebulized saline as the first challenge; administer increasing concentrations of methacholine in a stepwise fashion; after each administration, perform spirometry and look for a 20% drop in FEV_1; guidelines for test and its interpretation have been published by the American Thoracic Society; 4 mg/mL of methacholine is usually used as the threshold for a diagnosis of asthma

Limitations: may have false positive results in patients with an upper respiratory tract infection or in patients with extrinsic environmental allergies

Patient results: negative test; asthma is unlikely

Pulse oximetry: often used to assess patients with respiratory disorders; the "fourth vital sign;" requires a diode that emits a monochromatic light in the red range and a receptor; measures background absorbance during diastole and the augmentation observance of the red light that occurs during systole; this augmentation of light (the difference between the background measurement and the augmentation during systole) correlates with saturated hemoglobin; normal oxygen saturation is >90%; standard variance on this test is usually ±2%, but ±4% should be considered the standard variance in persons of color; standard variance increases when measurements are <90%; indicated for all patients suspected of having low oxygen saturation and for respiratory disease screening

Quality determination: ensure that the recordings are accurate; the patient's actual pulse should match the pulse on the device; pulse matching allows one to be certain that the instrument is properly detecting the patient's pulse; pulse oximeters generally have signal

indicators that tell signal strength and quality (waves, dots, or stars)

Limitations: errors in measurement are increased by skin pigmentation, nail polish, and poor perfusion of blood; ambient light can cause artifacts; only distinguishes between oxygenated and deoxygenated hemoglobin; if the patient has carboxyhemoglobin, methemoglobin, or some other hemoglobin species, this may cause inaccuracy; to determine presence of other hemoglobin moieties, perform an arterial blood gas and assess by co-oximetry

Patient results: pulse oximetry reading of 97% at rest

6-minute walk test: a test of exercise capacity for patients with respiratory illness; patients walk on a measured course as fast as they are able for 6 minutes and the total distance walked is measured; while walking, the patient's oxygen saturation is monitored

Indications: used to assess patients with COPD; the distance walked is incorporated into a metric called the BODE index (B — body mass index, O — degree of airway obstruction, D- severity of reported dyspnea, E — exercise, the performance on the 6-minute walk test); common outcome measure in studies assessing treatment for pulmonary hypertension; lung transplant centers use it in patient assessments; used by clinics to gauge treatment response and the need for pulmonary rehabilitation for a variety of conditions

Limitations: non-ambulatory patients cannot be assessed by this method; patients with musculoskeletal disorders may not be able to properly perform the test; the ability to perform may be affected by non-pulmonary respiratory disorders such as cardiac conditions

Patient results: our patient had robust exercise performance and function in her activities of daily living; she was not initially considered to require a 6-minute walk test

Chest X-ray: useful screening tool for patients with respiratory disorders and may indicate the cause of respiratory symptoms; allows monitoring pulmonary condition for progression; comparison with previous images allows for the identification of new findings, provides evidence for resolution of acute processes, and confirms the stability of chronic changes

Indications: assessment of patients with new chest symptoms or with previously identified abnormalities that are being monitored for stability or resolution; following certain medical procedures to evaluate for pneumothorax, other complications, or positioning of various medical devices; assessment of asymptomatic patients with a positive screening test for tuberculosis; should not be routinely performed in asymptomatic patients undergoing a pre-operative assessment; should not be used for routine screening for lung cancer in asymptomatic patients; should be avoided in pregnant patients; if required in a pregnant woman, appropriate shielding is needed

Limitations: a normal chest X-ray does not rule out serious disease, for example, asthma or pulmonary embolus (PE); limited resolution does not allow for careful study of the mediastinum and hilar structures; small lesions may be difficult to visualize; in the absence of prior studies, it may be difficult or impossible to determine the acuity of a specific finding; exposes patients to radiation

Patient results: our patient has new chest symptoms; chest X-ray shows a 1-cm right upper lobe nodular lesion

Chest computed tomography (CT) scans: used in the evaluation of patients with respiratory complaints; a high-resolution chest imaging technique; used in patients with chest disease to provide higher quality imaging; may be performed with or without contrast media; special protocols include pulmonary angiography to assess for pulmonary embolus; special high resolution techniques are commonly used to assess patients with interstitial lung disease; low-dose techniques are used to screen patients for lung cancer; providers are advised to seek expert advice to ensure the appropriate technique is requested

Indications: patients who have one or more abnormalities visible on a standard chest X-ray, so that images of higher definition are required; may be useful in patients prior to invasive procedures such as bronchoscopy, thoracentesis, or chest surgery; patients with chronic, severe, unexplained symptoms or test (eg, PFTs) abnormalities may undergo chest CT scan without prior chest X-ray; special cases exist where a specific type of chest CT scan is performed in patients with a normal chest radiograph and a high clinical suspicion of a chest disorder is present (eg, perform a chest CT pulmonary angiogram protocol in a patient with a normal chest X-ray and a high clinical suspicion of pulmonary embolism, eg, high d-dimer test or Wells score)

Low-dose CT scan for lung cancer screening: screening at-risk patients may lead to early diagnosis and improved outcome; carefully select patients to whom to offer this test based on a smoking history of at least 30 pack-years, an active smoker, a person who has quit smoking within the last 15 years, and age between 55 and 77; it is important that patients engage in shared decision-making processes and can manage screening costs (often not covered by insurance); if screening begins, it should be continued annually until a patient has quit smoking for 15 years; screening results in a relative lung cancer mortality reduction of 20% and a relative reduction of all-cause mortality of 6.7%; risks of screening include consequences of adventitious abnormal findings, radiation exposure, patient distress, overdiagnosis, increased costs

Limitations: findings from chest CT scan do not prove a diagnosis; confirmatory tests (eg, biopsy) are often needed; findings may require further CT imaging; radiation exposure can be significant, especially with multiple tests; some patients are allergic to radiocontrast media; patients with renal failure may suffer further injury with radiocontrast media; test is expensive; should be avoided in pregnant women, or shielding used if the test is medically needed

Patient results: had an abnormality on her initial chest imaging, so had a chest CT scan with contrast to image the mediastinal structures; demonstrated a spiculated right upper lobe nodule that was associated with a bronchus; paratracheal, right hilar, and subcarinal lymph nodes <1 cm were identified; high suspicion for bronchogenic carcinoma

Positron emission tomography (PET) scan: a nuclear medicine imaging technique that is helpful in the

assessment of the extent and stage of a suspected malignancy; fludeoxyglucose labeled with ^{18}F is administered; this compound is taken up in metabolically active tissues; radioactive decay with the emission of a positron leads indirectly to the production of photons in the gamma range, which are detected and used to form imaging of the tissues, with more intense radiation produced in more metabolically active areas; indicated in patients suspected of malignancy; used to see extent of disease, localize neoplastic tissues for biopsies, and assess for staging and eventual treatment

Limitations: expensive; pulmonary nodules <1 cm are below the limits of detection; inflammatory diseases of the lung and mediastinum may lead to false positive results

Patient results: PET scan demonstrated that the right upper lobe nodule has positive uptake; minimal to no uptake in mediastinal lymph node areas

Fiberoptic bronchoscopy: a commonly used tool to examine endobronchial anatomy; can be used to obtain biopsies under direct vision, to obtain transbronchial biopsies with the use of fluoroscopy, and to obtain specimens by cytology brush, needle, or washing; indicated in patients with suspected lung cancer to establish the diagnosis; used to assess airway anatomy and perform biopsies to confirm the extent of the disease

Indications: examination of the patient's bronchial anatomy to determine if tumors or foreign bodies are present, and to examine the airways for other pathology to include the cause of hemoptysis; in patients with suspected lung cancer, indicated to assist with diagnosis and determine the extent of disease

Limitations: requires conscious sedation; ensure patients are stable for the procedure; complications may include bleeding, infection, and pneumothorax; does not offer specific treatment for lung cancer and can sometimes be skipped in favor of timely surgery; can offer palliation for patients who have advanced lung cancer, including laser ablation of tumors and stent placement to improve respiratory sufficiency

Patient results: a bronchoscopy revealed an endobronchial lesion in the right upper lobe that correlated with the lesion seen on X-ray and CT scan; biopsies demonstrated an adenocarcinoma of the lung

Endobronchial ultrasound (EBUS): allows for a cytologic assessment of structures adjacent to the airways, but not directly visible; may be used with bronchoscopy to perform biopsies of extraluminal structures; special bronchoscopes are required; large bore needles can be employed for core biopsies of adjacent structures; most commonly used to assess mediastinal lymph nodes in patients with cancer

Limitations: left-sided upper mediastinal lymph nodes, especially pre-vascular nodes, are difficult to access; specific expertise is required; a comprehensive visual examination of the airways may require the bronchoscopist to use both a standard bronchoscope and an EBUS bronchoscope

Patient results: no evidence of neoplasm was found in right paratracheal. subcarinal, or right hilar lymph nodes; she was treated with a right upper lobe resection as definitive therapy for her cancer

Asthma case presentation: Ms. Williams is a 25-year-old woman who has had asthma since adolescence; had good control with a low-dose inhaled corticosteroid and a short-acting beta agonist agent; spirometry recently revealed an FEV_1 to FVC ratio of 79%, which was reduced when compared with normals; had obstructive airway disease; only symptom is cough; over the last 4 months, she has noted worsening symptoms, especially with exercise; she is using her short-acting beta agonist daily and she finds that she especially needs to use this before and after exercise; she continues with her activities of daily living and can engage in most of her outside activities; has an elevated IgE level at 400 IU; she weighs 55 kg

Asthma: about 1 in 10 persons have asthma; high rates of emergency room visits and hospitalizations; more common among children, blacks, and Hispanics; women make twice as many emergency room visits as men, and about 1 visit in 10 results in a hospitalization; type 2 inflammation occurs in a subgroup of patients; as many as 50% of asthma patients have some degree of type 2 inflammation; important mediators of type 2 inflammation include interleukin (IL)-4, IL-5, and IL-13; other associated phenomena include elevated levels of blood and sputum eosinophils, serum IgE, and an increase in the fraction of exhaled nitric oxide; some new asthma medications target the specific features of type 2 inflammation; asthma is a heterogeneous disease and most patients note various triggers to asthma; manifestations (eg, degree of airway inflammation, the presence or absence of mucus plugging) and responsiveness to treatment vary among patients; challenge in the emergency room is deciding who can be discharged and who needs hospitalization; the development of a respiratory acidosis is an indicator that the patient may require close observation and monitoring

Types of asthma (not mutually exclusive): cough-variant asthma is asthma in which the patient principally coughs; our patient had cough as one of her only symptoms, so she might be said to have cough-variant asthma; in exercise-induced asthma, patients with asthma have symptoms that are principally associated with exercise; many patients with asthma have exercise as a trigger — that was true in our patient; exercise-induced asthma can overlap with the other types of asthma; allergic asthma implies that the patient has asthma symptoms with seasonal allergies as a trigger; these patients will often have exacerbations of their condition during times when pollen counts are high; many patients have an allergic component to their asthma; in occupational asthma, patients principally have symptoms associated with a work environment; occupational asthma can be associated with specific or non-specific triggers; specific triggers are elements within the work environment to which the patient is exposed that provoke asthma; these may include animal elements(dander, hair, etc.), chemicals, enzymes, metals, plant substances, and others; triggers may also be general irritants such as dust or smoke; treatments are the same as for all asthma, but it may also be important for the patients, to avoid the specific triggers in the workplace

Classification of asthma: based on severity of the clinical presentation; the National Heart, Lung, and Blood Institute (NHLBI) has developed guidelines for the diagnosis and treatment of asthma; adult patients with asthma should be divided into intermittent or persistent asthma; adults with intermittent asthma typically have

symptoms less than 2 times a month, normal spirometry between exacerbations, and require oral corticosteroids for treatment of an exacerbation <1 time a year

Persistent asthma: divided into mild, moderate, and severe categories depending on symptom severity; our patient had asthma symptoms daily that required treatment — moderate persistent asthma; she had some minor limitations to her activities — also a sign of moderate persistent asthma; recommended treatment varies according to these classifications

Implications for treatment: the NHLBI proposes step therapy for asthma; as patients with asthma have symptoms that are poorly controlled, one should increase or augment their dosage of medications in a stepwise fashion; guidelines are provided to discuss at which step the asthma treatment should start; when a patient has demonstrated stability at a certain step for several months, it may be prudent to decrease their treatment in a stepwise fashion; allows providers to increase or augment treatment in response to complaints and symptoms and minimize exposures to medications when they have improvement in their disease; for our patient who has moderate persistent asthma, it is recommended that the care is initially provided at step 3 — involves either treatment with a low-dose inhaled corticosteroid plus a long-acting beta agonist for control, or a medium-dose inhaled corticosteroid; our patient currently takes a low-dose inhaled corticosteroid; examples of low-dose inhaled corticosteroid treatment are a fluticasone HFA (hydrofluoroalkane) inhaler at a dose of 88 to 264 mcg daily in divided doses or budesonide at 180 to 540 mcg daily in divided doses; medium-dose inhalers include treatment with fluticasone HFA 264 mcg to 440 mcg daily in two divided doses or budesonide 540 mcg to 1,080 mcg daily in two divided doses; our patient was given a combination inhaler that continued her low-dose inhaled corticosteroid, but also included a long-acting beta agonist; we instructed her to continue her short-acting beta agonist bronchodilator as needed, but we advised her that her frequency of use would be used to assess her degree of control

Tools to assess asthma control: validated questionnaires that the patient can take (in provider's office or on-line) to help determine whether symptoms are well controlled; the Action Control Questionnaire (ACQ); the Asthma Control Test (ACT); the Asthma Therapy Assessment Questionnaire (ATAQ); we administered the ACT to our patient and she scored a 12; the score of 19 or less on the ACT indicates the patient's asthma symptoms may not be well controlled and medical advice should be sought; a score of <15 indicates that asthma is very poorly controlled; our patient's score indicated that she needed an augmentation of her regimen

Biologic agents for treating type 2 inflammation: omalizumab treats elevated IgE; indicated in moderate to severe asthma, allergies to aeroallergens, and an IgE level that is between 30 and 700 IU; the patient's weight is considered when developing a dosing regimen; omalizumab is generally given in a provider's office and appropriate monitoring must be used after the treatment; our patient may be a candidate for omalizumab if her asthma is not readily controlled by augmenting her stepwise treatment

Chronic obstructive lung disease (COPD): related to cigarette smoking and is common in many countries

Case presentation: Mr. Jones is a 55-year-old man who has a history of COPD; he had pulmonary function tests done, which reveals an FEV_1 to FVC ratio of 45%; this is consistent with severe obstructive lung disease; has a total lung capacity that is 125% of predicted, and a DLCO, which is 40% of predicted; he has a combination of obstructive lung disease and hyperinflation, which is consistent with a diagnosis of emphysema and COPD; had 3 episodes over the past year where he had shortness of breath, cough, and increased sputum production that were treated with prednisone and antibiotics; we consider these episodes to be exacerbations of COPD; Mr. Jones has been treated with a long-acting muscarinic antagonist and a short-acting beta agonist for his symptoms; he continues to smoke cigarettes; his resting oxygen saturation was 94%; a chest X-ray demonstrated hyperinflation and flattening of the hemidiaphragms

COPD risk factors: in developed nations, cigarette smoking is the most common risk factor; in emerging nations, exposure to smoke from cooking fires is a risk factor; requires the attention of a primary care provider or a pulmonary specialist; caused by multiple factors and is a heterogeneous disease; some patients have predominantly an emphysematous form of disease with mainly shortness of breath; others have a prominent cough and sputum production (chronic bronchitis)

COPD, emphysema, chronic bronchitis: terms are similar and related, but not exactly the same; COPD implies that a patient has chronic obstructive pulmonary disease with typical findings on spirometry; emphysema indicates destruction of lung tissue, in most cases from smoking, and is best identified by emphysematous changes in the lung on CT scan; emphysema patients commonly have obstructive lung disease; may also have hyperinflation and a reduced DLCO, like our patient; chronic bronchitis indicates a patient who has a chronic cough on most days for 3 consecutive months, with 2 such episodes of 3 consecutive months occurring in 2 contiguous years; chronic bronchitis, emphysema, and COPD may coexist in the same patient or one or more of the symptom complexes may be present in an individual patient

COPD classification: based on the GOLD Guideline, which is based on a classification scheme that includes findings based on spirometry, exacerbation history, and scores on a symptom-related, validated questionnaire; a patient such as ours with COPD and an FEV_1 to FVC of 45% would fall into a GOLD 3 classification, which is based on spirometry between 30% and 49%; classifications extend from GOLD 1 through GOLD 4; a system of classification based on both symptoms and exacerbations has been developed within the GOLD Guidelines; this scheme classifies patients as having Group A, B, C, or D in terms of the frequency of COPD exacerbations and the score on a validated questionnaire; in the COPD Assessment Test (CAT), scores <10 are considered to be associated with lesser disease, whereas scores >10 are associated with more severe disease; an mMRC (modified Medical Research Council)score between 0 and 1 is associated with lesser disease and an mMRC >2 is associated with more severe disease; group A is characterized by 0-1 exacerbation during the preceding year and a CAT score <10 or an mMRC

of 0-1; group B — 0-1 preceding exacerbations and an mMRC >2 or a CAT >10; group C — >2 exacerbations in the preceding year or >1 leading to hospital admission, an mMRC score of 0-1 and a CAT <10; group D — most severe group, >2 exacerbations per year and those who have an mMRC score >2 or a CAT score >10; our patient had a CAT score >10 and 3 exacerbations in the past year, which classifies him as group D

Mechanisms of development: complex; early theories suggest that patients with an underlying history of asthma are at greater risk of developing COPD if they were long-term smokers; there is some evidence that asthma patients who smoke may be at increased risk for lung problems, but not all patients who smoke and develop COPD have asthma; other theories suggest there may be an imbalance between elastases and anti-elastases in the lung; this is the case in alpha-1-antitrypsin lung disease, but there is no evidence that this is true in patients who develop COPD from smoking; is evidence that COPD patients have increased lung compliance and decreased elastic tissue with destruction of the elastin matrix of the lung; oxidative stress may also play a role

Smoking cessation: the most important treatment for Mr. Jones is to help him quit smoking; this is the greatest reversible risk factor in treating patients with emphysema; it should be engaged before all other treatments are considered; patients who are able to quit smoking may halt emphysema progression; smoking cessation counseling should be undertaken, and a patient should be offered nicotine replacement therapy or other pharmacologic interventions; most pharmacologic interventions are more effective when combined with counseling; important to help patient set quit date

COPD treatment: Mr. Jones should also be treated with medications that are specific for the management of COPD; upon his presentation to our clinic, he was taking a short-acting beta agonist and a long-acting muscarinic antagonist; other therapies may be advantageous; group A — smoking cessation and a bronchodilator such as a short-acting beta agonist; group B — a short-acting beta agonist and either a long-acting muscarinic antagonist or a long-acting beta agonist; if these patients have persistent symptoms, they may be treated with both; patients with frequent exacerbations may need to be treated more aggressively; group C — a long-acting muscarinic antagonist and/or a long-acting beta agonist, and consideration in some patients is given to the use of inhaled corticosteroids; group D — smoking cessation is important, and treat with all 3 types of controlling agents — an inhaled corticosteroid, a long-acting beta agonist, and a long-acting muscarinic antagonist; also should be given a short-acting beta agonist to treat acute symptoms

Exacerbation treatment: several therapies have emerged; none of the inhaled therapies has been shown to demonstrate longevity improvements or reduce mortality rates, but all of these agents have been shown to reduce the frequency of exacerbations, improve spirometric indices, and reduce symptoms

- Roflumilast: patients in Group D who continue to have symptoms and are felt to be at continued risk for exacerbation may benefit; helps patients with chronic bronchitis and an FEV_1 <50% predicted to improve rate of exacerbations; limitations include gastrointestinal intolerance, and frequent high cost
- Macrolide therapy: long-term macrolide use may be helpful in reducing COPD exacerbations; the typical agent is azithromycin at 250 mg either every other day, or 3 times weekly; this regimen improves the rate of COPD exacerbations; patients must be monitored, as they may develop problems with ototoxicity and hearing loss, and may be at risk for cardiac dysrhythmias; pretreatment assessment should include an ECG to check for prolonged QR interval and a hearing test; with chronic use, may be at risk for the development of resistant organisms in the airway; mechanisms by which macrolide therapy may work include not only its antibiotic effect, but also an anti-inflammatory effect
- Influenza vaccine: annual influenza vaccines and administration of the Pneumovax vaccine are important adjuncts because they may reduce COPD exacerbations
- Pulmonary rehabilitation: symptomatic patients should be offered pulmonary rehabilitation; will improve functional capacity and allow patients to tolerate their symptoms more readily
- Medication counseling: important to make sure patients using their medications appropriately and correctly
- Glucocorticoids: some practitioners prescribe glucocorticoids to patients with COPD, but these agents have not been proven to be beneficial when provided as maintenance therapy for long-term use
- Exacerbations: may be mild and treatable on outpatient basis, but may require emergency room visits, hospitalization, or ICU care; medications which may be effective include nebulized short-acting bronchodilators (short-acting muscarinic antagonists or beta agonists); in contrast to the lack of evidence for glucocorticoids on a chronic basis to improve COPD, the use of short-term glucocorticoid treatments to treat exacerbations of disease can be useful; there is evidence that glucocorticoids for treating COPD exacerbations reduce exacerbation rates, shorten recovery time, improve lung function, shorten duration of hospitalization, and increase the time to the next exacerbation; a typical dose would be prednisone at 40 mg for 5 days
- Antibiotic use in exacerbations: shortens the duration of an exacerbation and may increase the time to the next exacerbation; most practitioners limit the use of antibiotics to those patients who have increased dyspnea and purulent sputum; routine use in COPD exacerbations may not improve outcomes and may lead to the development of resistant pathogens
- Supplemental oxygen: should be used based on patient's degree of hypoxemia; patients developing respiratory failure should be treated with positive pressure mask ventilation; shown to lead to improvement of shortness of breath and respiratory symptoms in patients with a COPD exacerbation; reduces the rate of intubation and mechanical ventilation; contraindications to the use of non-invasive ventilation include inability to fit the mask, inability of the patient to cooperate with mask ventilation, facial or head trauma, vomiting; when patients develop respiratory failure and fail mask ventilation, intubation and mechanical ventilation

should be considered; patients intubated and treated with mechanical ventilation for a COPD exacerbation usually have good outcomes if they can be liberated from mechanical ventilation after a few days

Lung transplantation: patients with severe COPD who develop high oxygen requirements and are extremely limited by symptoms of dyspnea may be considered; the lung transplant evaluation should be conducted with a center experienced in COPD patients; consider COPD patients for transplantation if they are under 65 years of age, have relatively few comorbidities, and have maintained smoking cessation for at least a year

Palliative care: should be considered in patients who have very severe obstructive disease by spirometry and are very limited by their dyspnea in terms of their ability to function; palliative care may be an optimal outcome in a person with end-stage disease

Referral: patients should be referred to a pulmonary specialist if they have frequent exacerbations, if they have severe obstruction by spirometry, or if they have the need for advanced therapies (eg, advanced therapies to prevent COPD exacerbations, the need for oxygen treatment, or the need for pulmonary rehabilitation); patients with severe COPD can be co-managed by a PCP and a pulmonologist

Suggested Reading

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Pulmonary Disease: Bronchiectasis and Cystic Fibrosis, Diffuse Parenchymal Lung Disease, Occupational and Environmental Lung Disease, Pleural Disease, and Pulmonary Vascular Disease

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Bronchiectasis: obstructive lung disease; spirometry detects early mild to moderate airflow obstruction, later becoming more severe; defined as irreversible pathologic dilation of bronchi or bronchioles resulting from infectious process, impaired mucus drainage, or abnormality in antimicrobial defenses; often, underlying cause leads to inflammation, dilation of bronchi or bronchioles, and bacteria colonize in airways; cycle of impaired mucus drainage because of dilated bronchioles, leading to more bacteria, more bronchiectasis, and more obstructive lung disease; *patterns* — focal bronchiectasis (*ie*, small area) often related to extrinsic airway changes (*eg*, compression from tumor, foreign body within airway, scar from previous trauma, or pneumonia); diffuse pattern associated with underlying systemic or infectious disease

Underlying associated disease: divided into upper-lobe–, midlung–, and lower lung–predominant disease

Upper lobe: cystic fibrosis (CF), allergic bronchopulmonary aspergillosis, and associated autoimmune or connective tissue diseases and syndromes (*eg*, rheumatoid arthritis [RA], scleroderma, systemic lupus erythematosus [SLE], sarcoidosis, Sjögren syndrome, inflammatory bowel diseases)

Midlung (Lady Windermere syndrome): collapse of right middle lobe; secondary to bronchiectasis and mucus plugging from nontuberculous mycobacteria, particularly *Mycobacterium avium intracellulare*, complexes that colonize area

Lower lobe: related to chronic recurrent aspiration, end-stage fibrotic diseases (*eg*, usual and nonspecific interstitial pneumonias [NSIP]); "traction bronchiectasis"; related to scar from fibrosis, pulling airway open; recurrent infections associated with immunodeficiency syndromes (*eg*, immunoglobulin deficiencies, HIV infection, hyper-IgE syndromes, common variable immune deficiencies)

Others that do not fit into above categories: primary ciliary dyskinesia, postradiation fibrosis

Diagnosis: chronic cough and purulent sputum; recurrent pneumonias, crackles, maybe digital clubbing; smokers or nonsmokers; high-resolution computed tomography (CT) scanning definitive; once confirmed, seek underlying cause; narrow differential based on location, focal vs diffuse; look for chronic bacterial or mycobacterial infections, rule out immunodeficiencies and HIV, look for hyper-IgE syndromes, assess for connective tissue diseases (*eg*, SLE, RA); if high clinical suspicion and history, evaluate for alpha-1 antitrypsin and CF; >50% of cases idiopathic

Treatment: mainstays of therapy to reduce symptoms, improve quality of life, and prevent and treat acute exacerbations; *symptom reduction* — airway clearance and anti-inflammatory medications; hypertonic saline thins secretions; airway-clearance devices (*eg*, Vest, Acapella, Aerobika); anti-inflammatory therapies (*eg*, inhaled or systemic glucocorticoids); macrolide antibiotics (*eg*, azithromycin [Zithromax, Zmax, Z-Pak); for COPD, inhaled corticosteroid plus short- or long-acting bronchodilator if ≥2 exacerbations/yr; azithromycin has demonstrated clinical benefit; rule out nontuberculous mycobacteria prior to starting azithromycin to avoid fostering resistance; no role for inhaled antibiotics unless >3 episodes/yr; alternate on and off on monthly basis or alternate antibiotics to decrease bacterial load; *pulmonary rehabilitation programs* — lead to improved exercise capacity and fewer outpatient and emergency department (ED) visits

Treatment of acute exacerbation: identify by changes in baseline symptoms; more sputum production or different color, hemoptysis, wheezing, shortness of breath, decline in lung function; start empiric antibiotic therapy unless culture data support narrowing; target against gram-negatives and *Staphylococcus aureus*; depending on symptom severity, start intravenous (IV) antibiotics, 10- to 14-day course (oral or IV)

CF: obstructive lung disease; results from mutations in CF transmembrane conductance regulator (CFTR) gene; causes epithelial mucus dehydration, viscous secretions, occlusion of respiratory airways, persistent airway infections, progressive tissue destruction; multisystem disease; CFTR protein present throughout body, so impaired chloride transport, which leads to thicker secretions in lungs, sinuses, pancreas, gastrointestinal (GI) tract (including liver and intestines; most babies with CF present with meconium ileus), and vas deferens in males; autosomal recessive disorder; ~70,000 people affected worldwide; 35,000 in US; ~7% to 10% remain undiagnosed until adulthood

Diagnosis: in adult, obscured because of atypical or delayed presentation; symptoms or signs (*eg*, recurrent pancreatitis, male infertility, chronic sinusitis, severe nasal polyposis, nontuberculous mycobacterial infection, allergic bronchopulmonary aspergillosis, bronchiectasis, and positive sputum cultures for

bacteria not community acquired [*eg*, *Burkholderia cepacia*, *Pseudomonas aeruginosa*, *Stenotrophomonas*, and *Achromobacter*]); diagnosis based on clinical findings with biochemical (sweat testing mainstay of laboratory confirmation) or genetic testing

Sweat testing: put pilocarpine on skin, collect sweat, analyze chloride; 0 mmol/L to 39 mmol/L, unlikely CF; 50 mmol/L to 59 mmol/L, intermediate; ≥60 mmol/L indicative of CF; once confirmed, undergo CFTR mutational analysis; comorbidities include diabetes from pancreatic dysfunction, infertility from azoospermia (~95% of men), osteoporosis from malabsorption of fat-soluble vitamins, liver disease

Management: airway clearance, antibiotic therapies, nutritional and psychosocial support; objectives of treatment maintaining long health, controlling and minimizing impact on organs; most patients die from underlying lung disease; pulmonary exacerbations markers of lung function decline, decreased quality of life, increased morbidity; *mucolytics or hydrating agents* — thin mucus and airway clearance devices remove mucus; mainstays of therapy, dornase alfa (Pulmozyme) and hypertonic saline; *antibiotics* — oral macrolide antibiotics (*eg*, azithromycin) in patients with *P aeruginosa* colonization and frequent exacerbations; nutritional support

Treatment of exacerbations: most on inhaled antibiotics for alternating mos if *Pseudomonas* present; often inhaled tobramycin (Tobi, *etc*), colistin (Coly-Mycin), and aztreonam (Azactam, Cayston); for exacerbation, treat with IV or oral antibiotics, depending on severity and resistance patterns; medications tailored towards gram-negative rods, possibly methicillin-resistant *S aureus* (MRSA); CFTR modulator drugs include ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), and tezacaftor/ ivacaftor (Symdeko); start drugs based on CFTR mutations; improve forced expiratory volume in 1 sec (FEV_1), weight, and BMI; decrease exacerbations

Diffuse parenchymal lung disease: heterogeneous group of disorders; in general, not infectious; present with dyspnea, cough, diffuse imaging abnormalities; 30% to 40% idiopathic; classification hinges on known causes or associations vs idiopathic; pathology specimens gold standard for diagnosis; histopathologic patterns correlate with disease prognosis and treatment responses

Diagnosis: 5 groups; 4 overlap with idiopathic group; 1. connective tissue diseases; 2. drug induced; 3. occupational or exposures; 4. primary; 5. idiopathic; broken down into acute or subacute, and more chronic and indolent types; HRCT scanning diagnostic tool of choice; patterns correlate with pathologic findings on open lung biopsy; may not need lung biopsy with thorough history, HRCT scan, positive or negative serologic testing; pulmonary function testing (PFT) can be helpful

Known causes: tobacco smoke can be associated many of these disorders, including idiopathic pulmonary fibrosis (IPF); some develop only in individuals with active smoking history (*eg*, respiratory bronchiolitis-associated interstitial lung disease and desquamative interstitial pneumonia); smoking cessation primary management; in severe disease, glucocorticoids used, but benefit uncertain

Connective tissue diseases: high prevalence of pulmonary manifestations in people with known connective tissue disease; often, lung disease identified after established diagnosis of connective tissue disease; identify any underlying autoimmune disorder; pulmonary disease primary cause of mortality in systemic sclerosis (SSc); cyclophosphamide may have short-term benefit; control gastroesophageal dysmotility and avoid aspiration with further lung injury; RA commonly has associated lung disease; patients with RA and lung disease treated with glucocorticoids and other disease-modifying agents

Occupational or exposure: hypersensitivity pneumonitis results from immunologic response to repetitive inhalation; common sources include thermophilic actinomycetes, fungi, and bird droppings; *acute form* — usually presents within 48 hours of high-level exposure; fever, flu-like symptoms, cough, shortness of breath; HRCT scan shows ground-glass opacities in central lobular micronodules predominantly in upper and midlungs; treatment, removal from exposure; hallmark, recurrence of symptoms with exposure; history helps identify cause; *subacute and chronic forms* — more chronic, low-level exposures to inhaled antigens; bird fancier's disease classic example (*eg*, people who raise birds or have chronic exposure); cough, dyspnea, malaise, weight loss; HRCT shows centrilobular micronodules, septal thickening, fibrosis; treatment, remove offending antigen; glucocorticoids in patients with severe symptoms or evidence of fibrosis

Drug induced: consider when diffuse abnormalities on chest imaging, especially if history of use of certain drugs or chemotherapy; classic drug-induced lung syndromes seen with amiodarone (Cordarone, Nexterone, Pacerone), methotrexate (Trexall, *etc*), nitrofurantoin (Macrodantin, *etc*), and bleomycin (Blenoxane, Bleo 15k); symptoms can develop acutely after starting drug or present subacutely; discontinue medication and use glucocorticoids

Radiation-induced parenchymal lung disease: caveat, symptoms of acute radiation pneumonitis occur 6 wks to 12 wks after exposure; nonanatomic, sharp line defines area between what was or was not in radiation port; treatment determined by symptom severity; if evidence of severe disease with organizing pneumonia, benefit from glucocorticoids; in milder disease, inflammation can probably resolve without much lung destruction

Primary: *sarcoidosis* — multisystem granulomatous disease of unclear cause with predilection for lungs; pulmonary involvement occurs in >90%; most asymptomatic and disease discovered incidentally; classified based on radiographic pattern; Stage 0, normal radiography; Stage 1, hilar lymphadenopathy with normal lungs; Stage 2, hilar lymphadenopathy with abnormal lungs; Stage 3, no lymphadenopathy, but abnormal lungs; Stage 4, lungs with fibrosis and architectural distortion; diagnosis of exclusion; biopsies show noncaseating granulomatous disease; biopsy not warranted if completely asymptomatic with bilateral lymphadenopathy; *Lofgren syndrome* — bilateral hilar lymphadenopathy, migratory polyarthralgia, erythema nodosum, fever; treat with glucocorticoids; *Heerfordt syndrome* — anterior uveitis, parotitis, fever, facial nerve palsy; *treatment* — limited to patients with symptoms of organ dysfunction; no guidance for initiation of

specific glucocorticoids; steroid-sparing agents may be required; tapering regimens prolonged and based on attributable symptoms or physiologic metrics with frequent follow-up (*eg*, chest imaging, spirometry); *lymphangioleiomyomatosis (LAM)* — rare; occurs in women sporadically or associated with tuberous sclerosis; diffuse cystic lung disease from infiltration of smooth muscle cells in pulmonary parenchyma; genetic mutations lead to mechanistic target of rapamycin (mTOR) pathway activation; diagnosis based on imaging with diffuse, thin-walled cyst; often spontaneous pneumothorax, angiomyolipoma, and elevated vascular endothelial growth factor D; immunosuppression with sirolimus (Rapamune) limits progression

Idiopathic: acute or subacute diffuse parenchymal lung diseases (*eg*, cryptogenic organizing pneumonia [COP] and acute interstitial pneumonia [AIP]) and chronic and indolent forms (*eg*, IPF and NSIP)

COP: proliferation of granulation tissue within alveolar ducts, alveolar spaces, and surrounding chronic inflammation; known causes include acute infections and autoimmune disorders (*eg*, RA); includes patients with pattern but no clear associated cause; hallmark, unrelenting pneumonia; often presents with symptoms of 6 to8 wks' duration that can be confused with community-acquired pneumonia; resembles migratory infiltrates; looks like pneumonia with bilateral, diffuse, alveolar opacities and normal lung volumes; may have large nodules or masses in periphery; if nonspecific imaging findings and no improvement with antibiotics, bronchoscopy or lung biopsy establishes diagnosis; prognosis favorable; often responds to glucocorticoids; need thorough exam and careful review to ensure no underlying connective tissue disease; some have recurrence with dose tapering; some will need long-term immunosuppressive therapy

AIP: mimics acute respiratory distress syndrome (ARDS); develops rapidly over days to wks, resulting in progressive hypoxemic respiratory failure; biopsy shows diffuse alveolar damage; need careful history to ensure no aspiration, sepsis, pneumonia, or inhalation injuries that may be amenable to treatment; poor prognosis; treat with glucocorticoids; treat like patient with ARDS (low — tidal-volume ventilation) and avoid complications of critical illness; high mortality rates (~50%); patient who recovers from initial illness may relapse or develop chronic lung disease secondary to fibrosis

IPF: most common idiopathic interstitial pneumonia; rarely diagnosed in individuals aged <60 yrs; gradual onset of dyspnea and cough over mos to yrs; physical exam shows dry inspiratory crackles at bases; most have digital clubbing; PFT shows restrictive abnormality with reduced diffusing capacity; exclude other causes of fibrotic lung disease; if HRCT shows definitive usual interstitial pneumonia (UIP) pattern, diagnosis established; UIP pathologic diagnosis, IPF clinical diagnosis; HRCT shows basal- and peripheral-predominant septal line thickening with traction bronchiectasis and honeycomb changes (UIP pattern); poor prognosis, with estimated survival of 3 yrs to 5 yrs; variable disease course; avoid anything that could precipitate acute decline (*eg*, procedures and infection); most common cause of death respiratory failure; consensus statement recommends against mechanical ventilation for patients with acute respiratory failure from progression or acute exacerbation because recovery rare; treatment primarily supportive; in past, anti-inflammatory therapy (but associated with increased mortality); nintedanib (Ofev) and pirfenidone (Esbriet) focus on extracellular matrix and myofibroblasts that lead to fibrosis; nintedanib, tyrosine kinase inhibitor that blocks pathways that lead to activation of fibroblasts; pirfenidone regulates transforming growth factor (TGF)-beta and tumor necrosis factor (TNF)-alpha; lung transplant only curative treatment

NSIP: predominantly lower lobes; affects younger patients and strongly associated with connective tissue disease; many have SSc; may be diagnosed with idiopathic NSIP prior to diagnosis of autoimmune or connective tissue disease; patients need continued surveillance for connective tissue disease; prognosis for patients with underlying autoimmune disorder better than for those with IPF; more severely affected pulmonary function and more extensive disease on CT imaging portend worse prognosis

Occupational and environmental lung disease: identify key elements of exposure history and conditions that increase clinical suspicion of occupational lung disease

Clinical presentation: highly variable, dependent on particular exposure; clinical manifestations range from rhinitis, asthma, chronic obstructive pulmonary disease (COPD), to severe restrictive diseases; symptom onset can be acute (*eg*, reactive airway disease) or subacute and have significant latent period (*eg*, asbestosis); factors that raise index of suspicion for occupational lung disease include patient's raising concern about possible exposures at work (*eg*, temporal relationship to clinical symptoms and work? symptoms better during or after work? do symptoms abate or improve with time away from workplace?); similar symptoms in coworkers; known respiratory hazards at work that could be identified from material safety data sheets; failure to respond to initial therapy or symptoms further exacerbated by returning to work; onset of respiratory disorder without typical risk factors not fitting clear pattern; clustering of disease in geographic area possibly related to exposure; need historical details and comprehensive occupational history; identification of specific exposures, as well duration and concentrations, helps facilitate exposure-related documentation (*eg*, workers' compensation); management principle, prevention (*eg*, workplace interventions to avoid exposures) and early identification of coworkers possibly at risk

Asbestos-related lung disease: commonly associated with construction, automotive servicing, shipbuilding, mining industries; asbestos use in US eliminated since peak in 1980s; because of long latency period between exposure and disease development (15-35 yrs), still see manifestations of asbestos exposure; major public health concern in developing world; parietal plaques most common findings; fibers migrate throughout lung and deposit in plaques; diffuse parenchymal lung disease caused by asbestos (asbestosis) secondary to extent of fiber burden; starts as alveolitis; if low fiber burden, resolves spontaneously; with higher burden,

more inflammatory and cytotoxic agents released by macrophages, which recruit fibroblasts, and fibrotic lung disease develops

Asbestos-related pleural diseases: pleural plaques most common form, characterized by smooth, white, raised, irregular lesions affecting parietal pleura; asymptomatic in absence of parenchymal disease; usually incidentally found; pleural fibrosis can be localized or diffuse; when diffuse, leads to symptomatic restrictive lung disease; limited treatment options; little benefit to surgical removal of pleural layer; pleural effusions occur either early or late after exposure; pleural fluid exudative and often hemorrhagic, may have eosinophils; exposure increases risk of lung cancer and mortality, particularly when combined with smoking

Silicosis: spectrum of fibrotic lung diseases related to inhalation of silica dust; affects workers in industries that process silica-containing rock or sand; lesions lead to progressive fibrosis with accelerated or latent course; tuberculosis (TB) incidence increased; symptoms of silicosis should prompt evaluation for concomitant infection; once fibrotic disease develops, no therapeutic interventions alter disease course; goal to remove from environment with silica dust and provide smoking-cessation counseling; symptomatic treatment includes inhaled bronchodilators, antibiotics, supplemental O_2, and lung transplant if appropriate

Pleural disease: 2 main types of abnormalities, increased fluid (pleural effusion) or air (pneumothorax)

Pleural effusions: most common disorder affecting pleura; occur as result of increased fluid formation or decreased fluid resorption; vast majority in US result from heart failure, pneumonia, or malignancy; worldwide, most result from TB; radiographs show pleural effusion when 200 mL of pleural fluid present; lateral films abnormal when ~50 mL of pleural fluid present; thoracic ultrasound mainstay of imaging

Simple vs complex: ultrasound characteristics can define; simple effusion, fluid in pleural space, with homogeneous echo texture seen in most transudative effusions; complex effusion, echogenic with substations or loculations, and usually exudate; use bedside ultrasound when performing thoracentesis to enhance accuracy and safety; gross fluid appearance serous, serosanguineous, hemorrhagic, or purulent; bloody fluid often seen with malignancy, pulmonary embolism (PE), lung infarction, trauma, benign asbestos effusion, or postcardiac injury syndrome; purulent fluid seen with empyema or lipid effusions; odor can guide if anaerobic infection or urinothorax; diagnosing fluid as transudate or exudate narrows differential diagnosis and informs other testing; Light's criteria (3 criteria, protein or lactate dehydrogenase [LDH] in fluid and serum)

Exudate criteria: pleural fluid total protein to serum total protein >0.5, pleural fluid LDH to serum LDH >0.6, or pleural fluid LDH >two-thirds upper limit of normal for serum LDH; other studies include cell count with differential, pH, glucose levels, culture, and cytology if malignancy suspected; additional testing based on clinical suspicion includes amylase, cholesterol, triglycerides, acid-fast bacilli (AFB), and *Mycobacterium tuberculosis* cultures; based on fluid analyses, transudates usually result of imbalance between hydrostatic and oncotic pressure, whereas exudates primarily from inflammation and impaired lymphatic drainage

Common causes of transudates and exudates: *transudates* — heart failure, hepatic hydrothorax, nephrotic syndrome, hypoalbuminemia, trapped lung, urinothorax, atelectasis, peritoneal dialysis; *exudates* — parapneumonic effusions, malignancy, PE, TB, autoimmune diseases (*eg*, RA, SLE), benign asbestos effusion, postcoronary artery bypass, pancreatitis, other drugs; cell counts with differential helpful in narrowing diagnosis; if high red blood cell count, consider hemothorax if pleural fluid hematocrit >50% of peripheral hematocrit; >50,000 nucleated cells signifies complicated parapneumonic effusion or empyema; if ~10,000, related to pneumonia, acute pancreatitis, SLE; lymphocyte count >80% in pleural fluid suggests TB, lymphoma, chronic rheumatoid pleurisy, sarcoid; glucose <60 common for rheumatoid pleurisy, complicated parapneumonic effusions, empyema, malignant effusion, tuberculous pleurisy, SLE pleuritis, or esophageal rupture; with decreased glucose, may also see pH <7.3; in suspected pleural infection, pH <7.2 should be treated with drainage (never let sun set on empyema); fluid amylase elevated if pleural fluid-to-serum amylase ratio >1, suggesting pancreatic disease, esophageal rupture, or malignant effusion; pleural fluid triglycerides >110 mg/dL characteristic of chylothorax, and <50 mg/dL reasonably excludes this diagnosis; tuberculous effusions common problem worldwide; adenosine deaminase elevated in most of these effusions; 95% sensitivity; *treatment* — in most cases, drain via thoracentesis; drain as dry as possible until patient coughs or has pain; parapneumonic effusions and empyemas need additional intervention (*eg*, chest tubes)

Parapneumonic effusions: exudative pleural effusions that occur adjacent to bacterial pneumonia and result from migration of fluid across pleura as result of inflammation; often sterile; small, uncomplicated, and improve with resolution of pneumonia; if pneumonia bacteria invade pleural space, complicated parapneumonic effusion or empyema results; complicated parapneumonic effusion results in decreased pH and glucose levels; empyema represents clear infection of pleural space with presence of pus; pleural effusions on chest radiograph ~1 cm deep should be sampled; if pH <7.2 or glucose <60 mg/dL, place thoracostomy tube; *treatment* — for uncomplicated parapneumonic effusions, pH >7.2 or glucose >60 mg/dL; use antibiotics (with or without thoracentesis) to drain, and serial follow-up ultrasounds or chest X-rays to ensure resolution; for complicated parapneumonic effusion, pH <7.2 or glucose <60 mg/dL; use antibiotics, chest tube, and possibly debridement through video-assisted thoracoscopic surgery (VATS); for empyema, when bacteria seen on gram stain, growing from culture, or fluid looks like pus, pH <7, need antibiotics, chest tube placement, and consult with thoracic surgeon; tissue plasminogen activator (tPA) and dornase help decrease need for surgical debridement; instill tPA and dornase

into chest tube twice daily for ≥3 days and see if this improves fluid removal

Pneumothorax: air in pleural space; occurs spontaneously from trauma or iatrogenically; spontaneous pneumothorax further characterized as primary (without underlying lung disease) or secondary (with underlying lung disease); risk factors for primary spontaneous pneumothorax include smoking, tall stature, family history, Marfan syndrome, thoracic endometriosis; secondary spontaneous pneumothorax commonly associated with COPD; *management* — depends on degree of clinical compromise, size, primary vs secondary; manage large, hemodynamically significant pneumothorax (tension pneumothorax) with high-flow supplemental O_2, emergent needle decompression, and thoracostomy placement; management of primary spontaneous pneumothorax depends on size; if <2 cm on chest radiograph and minimal symptoms, manage with observation if reliable follow-up and easy access to care; aspirate if >2 cm on chest X-ray, breathlessness, and chest pain; if reaccumulation, insert small-bore chest tube; if clinical instability, regardless of size, need emergent needle decompression and chest tube; for secondary spontaneous pneumothorax, if <2 cm with minimal symptoms, admit to hospital for observation and supplemental O_2; if >2 cm on chest X-ray, breathless, or chest pain, insert small-bore chest tube

Pulmonary vascular disease: normal mean pulmonary artery pressure ~15 mm Hg; pulmonary hypertension (PH) defined by resting mean pulmonary artery pressure ≥25 mm Hg; without treatment, PH leads to right ventricular failure and death; progression highly variable and dependent upon disease origin and comorbidities

Classification system: 5 groups based on mechanisms, clinical presentation, and treatment approach; all termed PH; *group 1* — disease localized to small pulmonary arterioles, resulting in high pulmonary vascular resistance; referred to as pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease, or pulmonary capillary hemangiomatosis; *group 2* — PH from left-sided heart disease (*eg*, systolic dysfunction, diastolic dysfunction, valvular disease); *group 3* — PH from lung diseases or hypoxia (*eg*, COPD, ILD, sleep-disordered breathing); *group 4* — chronic thromboembolic pulmonary hypertension (CTEPH); *group 5* — PH with unclear or multifactorial causes (*eg*, hematologic [myeloproliferative] disorders; splenectomy; systemic disorders [*eg*, sarcoidosis, pulmonary Langerhans, lymphangioleiomyomatosis, vasculitides]; metabolic and other disorders [*eg*, tumor obstruction, fibrosing mediastinitis, chronic kidney failure]); vast majority of PH cases attributed to left-sided heart disease and hypoxic respiratory disorders (groups 2 and 3 most common)

Echocardiography: useful in evaluation of suspected PH; noninvasive estimation of pulmonary artery pressures and right heart function, and assessment of left heart; may underestimate true pulmonary artery pressures; consider right heart catheterization after normal echocardiogram if high index of suspicion for PH; therapy for groups 2 through 5 directed at underlying condition; advanced therapy for PH with vasodilators reserved for patients with PAH; may actually be harmful in groups 2 through 5

CTEPH: developed by small subset of patients who experience acute PE; thrombus incorporates into pulmonary artery endothelium and creates pulmonary vascular resistance and pressures, leading to PH

Diagnostic criteria: documentation of PH by right heart catheterization in absence of left heart pressure overload; imaging evidence of chronic thromboembolism; often detected with sensitive ventilation–perfusion (VQ) scanning; main therapy, anticoagulants; indicated in all patients to help prevent further thromboembolism; pulmonary thromboendarterectomy only definitive therapy

PAH: subdivided into 5 groups; 1. idiopathic, 2. heritable, 3. drug- and toxin-induced, 4. other diseases associated with PAH (*eg*, connective tissue diseases, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis, chronic hemolytic anemia), 5. persistent PH of newborn

Diagnostic evaluation: PAH most commonly encountered in association with other conditions; right heart catheterization required to confirm pulmonary hemodynamics and to determine response to vasodilator infusion; no curative treatments; targeted vascular therapies improves survival; goals of therapy, to reduce vascular pressures, control symptoms, and improve/maintain quality of life; supportive measures include diuretic therapy to combat volume overload, supplemental O_2 for hypoxemia, pulmonary rehabilitation; because of predisposition to pulmonary vascular thrombosis and embolism, anticoagulation recommended

Vascular-targeted treatments: calcium channel blockers for patients with acute vasodilator response at time of right heart catheterization; prostanoids (*eg*, epoprostenol [Flolan, Veletri], treprostinil [Orenitram, Remodulin, Tyvaso], iloprost [Ventavis]) supplement endogenous levels of prostacyclin; endothelin-1 receptor antagonists (bosentan [Tracleer] and ambrisentan [Letairis]) block action of endogenous vasoconstrictor and smooth-muscle mitogen endothelin; risk of liver injury, teratogenic; phosphodiesterase (PDE)5 inhibitors (*eg*, sildenafil and tadalafil) prolong effect of intrinsic vasodilator cyclic guanosine monophosphate (cGMP) by inhibiting hydrolysis by PDE5; reasonable initial therapies for mild to moderate disease; iloprost, inhaled medication, but requires frequent administration; epoprostenol administered parenterally via central venous infusion; first-line therapy in severe disease and in patients who progress despite oral therapy; consider lung and heart transplant when drug treatment unsuccessful

Suggested Reading

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Lung Cancer

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Solitary pulmonary nodules: radiographic opacity ≤30 mm; surrounded by aerated lung; not associated with atelectasis, hilar enlargement, or pleural effusions; focal pulmonary opacity >30 mm defined as lung mass, presumed malignant until proven otherwise; solitary pulmonary nodules usually asymptomatic, found either incidentally or on lung cancer screening tests; morphologically, classified as solid or subsolid; subsolid nodules subdivided into pure ground-glass nodules and part-solid ground-glass nodules; pure ground-glass nodules higher-density opacification, do not obscure underlying bronchovascular structures, no solid component inside; part-solid ground-glass nodules have both "ground-glass"–appearing components and solid components; pulmonary nodules can be benign or malignant; *benign etiologies* — nonspecific or old granulomas (most common), infective granulomas, benign tumors (*eg*, pulmonary hamartoma, lipoma, fibroma), vascular lesions (*eg*, pulmonary arteriovenous malformations), inflammatory lesions (*eg*, granulomatosis with polyangiitis [Wegener granulomatosis], rheumatoid arthritis, sarcoidosis, amyloidosis, and rounded atelectasis), rarely intrapulmonary lymph nodes and pulmonary infarcts; *malignant etiologies* — primary lung cancer (adenocarcinoma most common [50% of malignant nodules], squamous cell carcinoma [20% of malignant nodules]), solitary metastasis, carcinoid tumors

Pulmonary nodule evaluation: review current and prior imaging, estimating pretest probability of malignancy (to determine further testing indicated, *eg*, surveillance chest computed tomography [CT], positron emission tomography (PET) scan, biopsy); shared decision making with patient highly recommended; >1 nodule present, follow-up determined by largest lesion; many institutions utilize multidisciplinary team approach to address nodules

Review imaging: if prior image or images available, nodule stable for 2 years if solid nodule or 5 years if subsolid nodules, no further testing indicated

Pretest probability of malignancy: start with no prior imaging available; can be done either clinically or with predictive models; common model, Brock University Cancer Prediction Equation, includes several factors (*eg*, age, gender, family history of lung cancer, presence of emphysema, nodule size, nodule type, location in upper lobe, number of nodules, and presence or absence of spiculation); other models include Veteran's Administration Cooperative Model, Mayo Clinic Model, and assessing likelihood ratios; no data to prove model superiority

Risk factors: *age* — risk of malignancy increases with advancing age; 35 to 39 yrs, ~3% risk; 40 to 49 yrs, ~15% risk; 50 to 59 yrs, 43% risk; >60 yrs, >50% risk; *nodule size* — 2 mm to 5 mm, 1% risk of malignancy; 6 mm to 10 mm, 24% risk; 11 mm to 20 mm, risk 33%; ~21 mm to 45 mm, 80% risk; *border* — smooth or lobulated, nodule usually benign; irregular and spiculated, usually malignant; *calcification pattern* — central, laminated, diffuse, and popcorn calcifications generally benign; stippled and eccentric patterns often nonspecific

Hamartoma: benign; presence of fat in nodules evaluated on CT scan with attenuation of -40 to -120 Hounsfield unit (HU reliable indicator

Pretest probability guides additional testing: if low pretest probability, <5% risk of cancer, serial CT preferred; if intermediate pretest probability, 5% to 65% risk of malignancy, PET scan or transthoracic needle aspiration and bronchoscopy for central lesions recommended; if high pretest probability, >65%, invasive testing with surgery or excisional biopsy recommended

2017 Fleischner Society data risk guidelines: provide recommendations based on risk factors for lung cancer and lesion size; endorsed by other professional societies (*eg*, American College of Chest Physicians [ACCP], American College of Radiology [ACR]); Fleischner Society risk stratification includes both patient and nodule characteristics; low-risk group includes nonsmokers, younger age, smaller nodules with regular margins, and non-upper lobe location; high-risk group includes heavy smokers, older age, history of prior cancers, larger size with irregular margins, and presence of nodule in upper lobe

Management of solitary solid pulmonary nodule: *<6 mm* — low-risk group, no further follow-up; high-risk group, CT at 12 mos; *solid nodule 6 mm to 8 mm* — both low- and high-risk groups, surveillance CT at 6 to 12 mos; if unchanged, repeat chest CT in 18 to 24 mos; *solid nodule >8 mm* — both risk groups, contrast-enhanced PET, CT, or tissue sampling or CT at 3 mos, based on local expertise and patient preference; if PET negative for metabolic uptake, continued surveillance recommended; if moderate to intense uptake, further evaluation with staging, followed by surgery or chemotherapy and radiation; *growth of solid nodules* — defined as increase in diameter >2 mm, rounded to nearest mm; screening CT scans, both initial and follow-up, should be low-radiation dose, no contrast, contiguously thin (*ie*, 1-mm sections) on helical scanner to ensure both diagnostic accuracy and measurement reproducibility

Solitary subsolid nodules: most transient, usually from infection or hemorrhage; persistent subsolid nodules often represent adenocarcinoma-spectrum malignancies, including adenocarcinoma in situ, minimally invasive adenocarcinoma, and invasive adenocarcinoma; replaces previous term (no longer used) bronchioloalveolar carcinoma (BAC)

Approach to subsolid nodules: differs from solid nodules; requires longer monitoring approach because of slow doubling time (usually 400-800 days compared with other cancer types, with doubling times of 50-100 days); PET scans unreliable because of poor uptake; growth defined as increased attenuation, increase in size, or development of solid component

Fleischner Society guidelines: recommendations for pure ground-glass nodules; <6 mm, no further follow up required; ≥6 mm, repeat chest CT at 6 to 12 mos to confirm persistence, then repeat CT every 2 yrs for 5 yrs; part-solid nodules; <6 mm, no further follow-up required; ≥6 mm, repeat CT at 3 to 6 mos; if unchanged and solid component remains <6 mm, annual CT for 5 yrs

Lung cancer: leading cause of cancer death among men and women, both globally and in United States (US); annually, more people in US die of lung cancer than of colon, breast, and prostate cancers combined; second most common cancer in both men and women after prostate and breast cancers, respectively; worldwide, lung cancer occurred in approximately 1.8 million patients in 2012, caused estimated 1.6 million deaths; annually in US, approximately 225,000 patients newly diagnosed with lung cancer, causes ~160,000 deaths annually; overall 5-yr survival rates 15% to 20%; lung cancer (bronchogenic carcinoma) refers to malignancies originating in airways or pulmonary parenchyma; risk factors include smoking, chronic obstructive pulmonary disease (COPD), advanced age, prior radiation therapy, exposure to environmental toxins, pulmonary fibrosis, human immunodeficiency virus (HIV) infection, genetic factors

Smoking tobacco products: primarily cigarettes; most important risk factor for development of lung cancer; accounts for ~90% of all lung cancers; factors that increase risk in smokers include extent of smoking (*eg*, 40 pack-yr smoking increases risk to 20-fold compared with never-smoker); exposure to other carcinogenic factors (*eg*, asbestos) can have synergistic effect, up to 60-fold risk; pipe or cigar smoking also associated with increased risk; health care professionals should counsel on prevention and cessation of smoking to decrease mortality and morbidity associated with lung cancer; *passive (secondhand smoking) exposure* — may cause ≤25% of lung cancer among nonsmokers; risk may be increased in those with exposure prior to age 25 yrs; some individuals develop lung cancer without significant smoking (*ie*, <100 cigarettes in lifetime); in US, 10% to 15% of lung cancer occurs in nonsmokers; worldwide, 15% of men, 53% of women with lung cancer nonsmokers

Other risk factors: COPD has 3- to 6-fold increased risk of lung cancer independent of smoking; advanced age also risk factor (average age at time of diagnosis, 70 yrs); radiation therapy increases risk in patients treated for other malignancies (*eg*, Hodgkin lymphoma, breast cancer); environmental toxins include exposure to secondhand smoke, asbestos, radon in miners, metals (*eg*, arsenic, chromium, nickel), ionizing radiation, and polycyclic aromatic hydrocarbons; patients with pulmonary fibrosis have 7-fold increased risk, independent of smoking; incidence in HIV patients ~50% higher and ~2 to 4 times more frequent than those uninfected, after matching for age and gender; genetically, established familial risk exists, can affect both risk and prognosis; exact mechanism unclear

Screening for lung cancer: screening not recommended for all people, especially not for symptomatic patients; previously, screening not recommended, as chest radiography and sputum cytology did not reduce mortality; National Lung Screening Trial (NLST), 2011, changed practice; randomized trial comparing CT screening to chest radiography annually for 3 yrs to detect lung cancer in current or heavy smokers (*ie*, ≥30 pack-yr smoking history) or those who quit smoking within 15 yrs; trial enrolled >53,000 participants aged 55 to 74 yrs; trial demonstrated 20% reduction in lung cancer mortality in heavy smokers and 7% reduction in overall mortality; as result, United States Preventive Service Task Force (USPSTF) recommends annual lung cancer screening using low-dose CT scan for high-risk, current, or former smokers; criteria for screening based on inclusion criteria in NLST trial, including asymptomatic individuals aged 55 to 80 yrs with significant heavy smoking history; Centers for Medicare and Medicaid Services (CMS) approved for age 55 to 77 yrs

Lung cancer types: 2 major types, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); *NSCLC* — accounts for 80% of all lung cancers; histologic classes include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma; incidences of lung cancer based on histology; adenocarcinoma most common (32%); squamous cell carcinoma (29%); *SCLC* — 18%; *large cell carcinoma* — 9%; *unclassified and undifferentiated* — 17%; increased incidence of adenocarcinoma thought to result from introduction of low-tar filtered cigarettes in 1960s, although causality unproven

Adenocarcinomas: typically located peripherally; often found incidentally; metastasize early to brain, adrenals, and bones; adenocarcinoma spectrum includes adenocarcinoma in situ, minimally invasive, and invasive adenocarcinoma; can have mucinous, nonmucinous, and mixed components

Squamous cell carcinomas: located centrally or in hilar regions with local extension; can cause postobstructive pneumonia symptoms and thick-walled cavitations; most likely lung cancer to cavitate; strong correlation with smoking history

Large cell carcinoma: typically presents as peripheral mass with prominent necrosis; metastasizes to brain, mediastinum; can cause hoarseness and superior vena cava (SVC) syndrome

Small cell carcinoma: neuroendocrine tumor; extremely aggressive; almost exclusively caused by smoking; does not cavitate; commonly associated with paraneoplastic syndromes

Clinical manifestations of lung cancer: both NSCLC and SCLC present with similar clinical symptoms; manifestations can vary from asymptomatic to local

tumor effects and extrathoracic effects due to metastasis; only 5% to 15% asymptomatic at diagnosis; *local (ie, intrathoracic) effects* — cough, hemoptysis, chest pain, shortness of breath (most common symptoms of lung cancer); *pleural effusion, bony tenderness, or neurological findings with papilledema* — indicate advanced disease from extrathoracic effects; ~15% of patients have extrapulmonary symptoms at presentation

Paraneoplastic syndromes: seen in 10% of lung cancers, most commonly associated with SCLC; include clubbing, hypertrophic pulmonary osteoarthropathy (common with adenocarcinoma, but can be seen in all 3 NSCLC types), gynecomastia (commonly seen with large cell cancer), Cushing syndrome and syndrome of inappropriate antidiuretic hormone secretion (SIADH; commonly seen with SCLC type), hypercalcemia from production of parathyroid-like hormone (more common with squamous cell type); *lung cancer most common cancer associated with paraneoplastic neurologic syndrom*e — typically associated with SCLC; includes Lambert-Eaton myasthenic syndrome, peripheral neuropathy, cerebellar ataxia, limbic encephalitis, encephalomyelitis, autonomic neuropathy, retinopathy, opsomyoclonus; *vascular paraneoplastic syndromes* — include migratory superficial thrombophlebitis, venous thromboembolism, nonthrombotic microangiopathy, disseminated intravascular coagulation

Other rare paraneoplastic syndromes: polymyositis, dermatomyositis; *rare clinical manifestations of lung cancer* — SVC syndrome, commonly associated with small cell and large cell tumors; clinical manifestations include facial and head fullness, cough, dyspnea, stridor, hoarseness and dysphagia; physical exam may demonstrate distended neck veins with visible collaterals, facial and upper chest edema, plethoric appearance, cyanosis, and hypotension; in severe cases, cerebral edema, coma; most guidelines recommend accurate histologic diagnosis prior to starting therapy in SVC syndrome; lung cancers arising in superior sulcus invade brachial plexus, causing characteristic Pancoast syndrome, manifested by shoulder pain, Horner syndrome, bony destruction, and atrophy of hand muscles; Horner syndrome includes unilateral ptosis, myosis, anhidrosis, and enophthalmos (small, sunken eyes)

Diagnosis and staging of lung cancer: initial evaluation must include detailed history, physical exam, complete blood count, complete metabolic panel, and chest CT; in US, ACCP evidence-based clinical practice guidelines commonly utilized for diagnosis and management; *noninvasive staging workup* — pan CT of chest, abdomen, and pelvis with contrast; PET scan; magnetic resonance imaging (MRI) of brain; PET sensitivity 80%, specificity 88%, hence invasive staging needed (nonsurgical or surgical); nonsurgical methods include bronchoscopy with endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS); sensitivity of each 89%, when EBUS combined with EUS, sensitivity 91%; both EUS and EBUS have 100% specificity; in general, central tumors have good yield with bronchoscopy and related procedures, most mediastinal staging achieved with combined EBUS and EUS combined; for peripheral lesions, transthoracic needle aspiration recommended; surgical staging includes mediastinoscopy or video-assisted thoracoscopic surgery (VATS)

Definitive diagnosis: requires tissue histopathology; ACCP guidelines recommend in patients with suspected lung cancer, solitary extrathoracic site suspicious for metastasis, fine-needle aspiration biopsy of metastasis to help diagnosis and staging (*eg*, for suspected lung mass and liver or abdominal metastasis, perform biopsy on metastasis first)

Patients with advanced-stage disease on radiography: diagnosis and staging best accomplished with single invasive test at location that will establish both diagnosis and stage (*eg*, in patients with suspected lung mass and palpable supraclavicular lymph nodes, supraclavicular nodes must be biopsied, which can aid with both diagnosis and staging)

Pleural effusions: thoracentesis and pleural fluid cytologic evaluation help with diagnosis and staging; however, yield only 50%; if 2 thoracenteses negative, guidelines recommend proceeding to VATS or medical thoracoscopy; closed pleural biopsies not useful

Definitive staging: essential to guide treatment decision making and for prognosis; NSCLC staged based on 8 additional TNM staging criteria, considering characteristics of primary tumor (T), regional lymph node involvement (N), and metastatic disease (M); *T* (*tumor characteristics*) — range from T0 to T4, depending on size and invasion of surrounding structures; T0 indicates no evidence of primary tumor; Tis indicates carcinoma in situ; T1, tumor size <3 cm; T2, size 3 cm to 5 cm or tumor involves main bronchus, invades visceral pleura and associated with atelectasis, obstructive pneumonitis that extends into hilar region and involves part or all of the lung; T3, size 5 cm to 7 cm, involves separate tumor nodule in same lobe, tumor invades chest wall, phrenic nerve, and parietal pericardium; T4, tumor size >7 cm, with a separate tumor nodule in different ipsilateral lobe and tumor invades diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina; *N* (*regional lymph node involvement*) — range from NX to N3; NX, unable to evaluate lymph nodes; N0, no involvement; N1, involvement of ipsilateral peribronchial, hilar, or intrapulmonary lymph nodes; N2, involvement of ipsilateral mediastinal lymph nodes; N3, involvement of contralateral mediastinal, hilar, or ipsilateral or contralateral scalene or supraclavicular lymph nodes; *M* (*metastatic component*) — ranges from M0 to M1c; M0, no metastasis; M1a, separate tumor nodule in contralateral lobe, tumor with pleural or pericardial nodule, malignant pericardial or pleural effusion; M1b, single extrathoracic metastasis; M1c, multiple extrathoracic metastases

Staging by TNM characteristics: NSCLC can be staged clinically at Stages I to IV; after surgery, using pathology information, can be staged as pathologic TNM; pathologic TNM more definitive than clinical TNM staging; see eighth edition of TNM Lung Cancer Staging Table for overview of staging process; although TNM can also be applied to SCLC, simplified version that separates these patients into those with limited vs extensive disease more widely used; limited disease defined as disease limited to 1 hemithorax

and involvement of ipsilateral supraclavicular lymph nodes; presence of disease outside these locations defines extensive-stage disease

Assessment for treatment: includes pretreatment evaluation, obtaining pulmonary function tests, electrocardiogram (ECG), assessing functional status, and accurate staging; ACCP guidelines recommend obtaining pulmonary function test and radionuclide perfusion lung scanning to estimate predicted postoperative lung function; forced expiratory volume in 1 sec (FEV_1) and diffusion capacity (DLCO), commonly utilized parameters that correlate with severity of lung function; if predicted postoperative FEV_1 or DLCO >60%, patient cleared for surgery; if 30% to 60%, stair-climbing or shuttle-walking test performed; if <30%, cardiopulmonary exercise testing recommended; perioperative pulmonary rehabilitation recommended for the high-risk group; if ECG abnormal, further cardiac workup recommended; *functional status assessed by Eastern Cooperative Oncology Group (ECOG)* — scored from 0 to 5; 0, asymptomatic; 1, symptomatic but completely ambulatory; 2, symptomatic, but <50% in bed during day and not bed bound; 3, symptomatic >50% in bed, not bed bound; 4, bed bound; 5, death; 0 and 1 indicate good functional status and better tolerance for surgery and chemotherapy; *ACCP guidelines* — recommend multidisciplinary team approach using tumor board meeting with specialists including pulmonologists, medical oncologists, cardiothoracic surgeons, pathologists, radiologists, and radiation oncologists while diagnosing and staging of lung cancer; patient values and preferences influence diagnosis and therapeutic choices; important for primary care physicians to refer all lung cancer patients to these tumor board discussions

Treatment of SCLC: at diagnosis, SCLC generally systemic; 70% of patients have extensive disease at presentation and only 30% present with limited disease; treatment of limited SCLC, chemotherapy with platin-based regimens (*eg*, cisplatin with etoposide or carboplatin with etoposide, fewer side effects and well tolerated); generally, patients receive 2 cycles of induction and reassessed, then receive 2 to 4 more cycles for consolidation; in addition to chemotherapy, radiation indicated for limited SCLC; survival benefit of 5% to 7% at 2 yrs, 5% at 3 yrs; initial response rate in 65% to 90% of cases, complete response in 45% to 75%; median survival ~16 to 24 mos; 2-year survival of 40% to 50%; for patients with limited SCLC who achieve complete remission after initial treatment, prophylactic cranial irradiation recommended; 3-yr survival improves from 15% to 21%; for patients with extensive SCLC, platin-based chemotherapy administered similar to that for limited stage; median survival 6 to 12 mos, without treatment, 2 to 4 mos; 2-yr survival ~20%; 5-yr survival <5%; no benefit of radiation in this group, except palliative; in patients with good performance who have complete or good partial response to initial chemotherapy, prophylactic cranial irradiation and/or observation with brain MRI surveillance acceptable options

Treatment of NSCLC: *patients with clinical Stage I and Stage II NSCLC with no medical contraindications to operative intervention* — surgery curative; lobectomy preferred over sublobar resections for survival benefit; some require pneumonectomy; limited resections (*eg*, wedge, segmentectomy) reserved only for patients with decreased pulmonary function or comorbid disease; *patients with early-stage lung cancer but not surgical candidates* — can be treated with stereotactic body radiation, with similar outcomes; *patients with completely resected pathologic Stage IIa NSCLC with good performance status* — postoperative cisplatin-based adjuvant chemotherapy recommended; *patients with Stage I to II NSCLC who have positive bronchial margin after surgery* — postoperative radiation therapy indicated; 5-yr survival rate ranges from 56% to 90%, depending on stage; *patients with Stage III NSCLC with good performance status (ie, ECOG score 0-1)* — consider for curative intent of treatment; concurrent chemoradiotherapy preferred over sequential chemoradiotherapy; *patients with Stage III NSCLC with poor performance status (ie, ECOG score 3-4), and with multiple comorbidities* — palliative radiotherapy recommended; s*elect Stage IIIa patients with N2 disease only* — definitive chemoradiation therapy or induction therapy followed by surgery recommended; risk of recurrence, both local and distant, high after chemoradiation therapy (70%-90%); *Stage IV patients with metastatic disease* — in past, all patients with metastatic NSCLC treated with same chemotherapy regimen

Recent development of precision medicine: specific molecular and genetic targets discovered, resulting in more tailored treatment; ~15% to 30% of non-Asian patients and ~30% to 60% of Asian patients with adenocarcinoma have mutations in epidermal growth factor receptor (EGFR) gene; anaplastic lymphoma kinase (ALK) gene mutations present in 2% to 7% of US patients with NSCLC; patients with nonsquamous histology, particularly adenocarcinoma, testing for molecular alterations standard of care; testing for mutations in EGFR and for translocations involving ALK or receptor tyrosine kinase (ROS1) mandatory; *platinum-based doublet chemotherapy regimen* — indicated only if patient has good performance status (ECOG score 0 or 1); patients with poor performance status do not benefit from chemotherapy; *patients receiving palliative chemotherapy for Stage IV NSCLC* — choice of chemotherapy guided by histologic type; if EGFR mutation, initial treatment with gefitinib or erlotinib recommended based on superior response rate, progression-free survival, and toxicity profiles compared with platinum-based therapies; good response seen in nonsmokers, females, and people of East Asian heritage; *if ALK or ROS1 translocation identified* — initial treatment with crizotinib or alectinib recommended; *if no mutations* — in addition to platinum-based therapy, patients with adenocarcinoma may respond well to pemetrexed; *patients with squamous cell carcinoma* — respond better to gemcitabine; other commonly used second agents in this setting include paclitaxel, docetaxel, and vinorelbine; chemotherapy administered for 4 to 6 cycles; can be given in combination with bevacizumab, monoclonal antibody directed against vascular endothelial growth factor; when given in combination with platinum-based therapy for patients with NSCLC as first-line treatment, shown to improve both progression-free survival and overall survival; gemcitabine shown to improve progression-free survival;

pembrolizumab superior to chemotherapy in first-line treatment of patients with metastatic NSCLC who have programmed cell death ligand (PD-L1) expression >50%; higher response rate, progression-free survival, and overall survival when compared with standard chemotherapy; pembrolizumab and nivolumab also both more active than chemotherapy in second-line setting

Posttreatment surveillance: includes detailed history, physical exam, chest CT every 6 mos for first 2 yrs, then annually; smoking cessation indicated to decrease risk of second primary malignancy and to reduce comorbidity; patients should receive smoking-cessation counseling, advice, and pharmacotherapy; smoking cessation decreases risk of new primary lung cancers from 20% to 90%; risk steadily declines beginning 5 yrs after quitting, but never reaches incidence found in nonsmokers

Rare Lung Tumors

Carcinoid tumors: rare pulmonary tumor; low-grade neuroendocrine tumors accounting for 1% to 2% of all lung cancers; cigarette smoking not risk factor; most carcinoid tumors arise in proximal airways as endobronchial lesions and cause postobstructive effects, leading to cough, dyspnea, wheezing, hemoptysis; bronchial obstructions can lead to lobar atelectasis or recurrent episodes of postobstructive pneumonia in same pulmonary segments; carcinoid tumors often misdiagnosed as asthma or pneumonia, which may delay diagnosis; surgical resection often curative; 10-yr survival rates as high as 90%

Pulmonary metastases: lung, frequent site for metastatic disease from primary malignancies including, head and neck, colon, kidney, breast, thyroid, and melanoma; metastatic disease can present as solitary or multiple nodules; can also occur as lymphangitic spread, endobronchial lesions, pleural involvement, or tumor embolic phenomena; surgical resection may be appropriate with solitary pulmonary metastasis if identified without evidence of other metastatic disease

Mesothelioma: rare; insidious; exclusively caused by exposure to asbestos; arises from mesothelial cells lining pleura; has long latency (20-40 yrs); malignant pleural mesothelioma typically presents in advanced stages; asbestos fibers found in soil and rock, resistant to heat and combustion, commonly used in cement, ceiling tiles, pool tiles, automobile brake linings, and ship building; cigarette smoking not risk factor for malignant pleural mesothelioma; because of strict environmental control of asbestos, rate of mesothelioma in US steadily declining since 2000; common in males because of high-risk occupational exposures; *clinical manifestations* — nonspecific; include insidious onset of cough, weight loss, dyspnea, chest pain, dysphagia, and unilateral hemorrhagic pleural effusions; can affect peritoneum causing malignant ascites, abdominal distension, and bowel obstruction; clinical suspicion should arise if unilateral pleural thickening or exudative pleural effusion and history of asbestos exposure; initial evaluation includes chest CT with contrast, thoracentesis of pleural effusion, and closed pleural biopsy; if nondiagnostic, medical thoracoscopy or video-assisted thoracoscopy aids in diagnosis by direct visualization or cytologic confirmation; PET scans useful for staging; *treatment* — depends on extent of disease and patient factors and preference; may include multimodality approach with surgery (commonly extrapleural pneumonectomy), radiation therapy, and systemic chemotherapy; overall prognosis poor, median survival 6 to 18 mos, 5-yr survival <5%, similar to extensive SCLC

Mediastinal masses: mediastinum located in center of thoracic cavity, enclosed by sternum anteriorly, lungs and pleura laterally, vertebral column posteriorly; mediastinal tumors benign or malignant; mediastinum divided into anterior, middle, and posterior mediastinum (helps determine different pathologies unique to each compartment); some conditions (*eg*, thoracic aneurysm) can be present in any or all compartments; *anterior mediastinum* — lies between sternum and cardiac great vessels; most common mediastinal location of malignant tumors occur; *"4 Ts" common in this location* — thymoma, teratoma (or germ-cell tumor), teratolymphoma, and thyroid carcinoma; thymic lesions most common, associated with autoimmune diseases (*eg*, myasthenia gravis, which commonly presents with muscular weakness, fatigability, ptosis, diplopia, bulbar symptoms); 15% of myasthenia gravis patients may have thymoma; *masses in middle mediastinum* — attributed to lymphadenopathy secondary to lymphoma, sarcoid, or metastatic disease; other causes include bronchogenic cyst, pericardial cyst, hernia, or aortic aneurysm; *masses in posterior mediastinum* — include neurogenic tumors (*eg*, neurofibroma, schwannoma, meningoceles and spinal lesions)

Suggested Reading

MacMahon H et al: Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology.* 2017;284(1):228-43; **Nanavaty P et al:** Lung cancer screening: advantages, controversies, and applications. *Cancer Control*. 2014;21(1):9-14; **Rivera GA, Wakelee H:** Lung cancer in never smokers. *Adv Exp Med Biol.* 2016;893:43-57; **Sigel K et al:** Lung cancer in persons with HIV. *Curr Opin HIV AIDS*. 2017;12(1):31-8.

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Critical Care Medicine

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Prompt identification of critically ill patients: follow a simple algorithm such as the ABCDEs to rapidly assess every patient; A — airway, is the patient able to participate in the gas exchange, is there any stridor or upper airway obstruction, is the mental status poor, affecting the ability to protect the airway; it is paramount to recognize the need for intubation, keeping in mind that this can precipitate hemodynamic collapse; B — breathing, assessing for respiratory rate, use of accessory muscles, symmetry of breath sounds, ability to complete sentences, and identification of a life-threatening pneumothorax; C — circulation, assessing for signs of malperfusion, symmetry of pulses, optimizing volume status and administering fluids, and then reassessing for volume response; D — delivery of oxygen or disability regarding neurological examination, Glasgow Coma Scale (GCS), mental status, baseline neurological status; E — endpoints of resuscitation such as mean arterial pressure (MAP), central venous pressure (CVP), urine output, central venous oxygen saturation (ScvO2), lactate, bicarbonate; E can also be used for exposure, recognizing that hypo- and hyperthermia can be caused by the provider; allow the patient to be covered as much as possible; numerous scoring systems exist to help identify ill patients; SOCCER (signs of critical conditions in emergency response) uses 5 early and 5 late signs to assess the critical nature of the patient's condition; the APACHE (Acute Physiological and Chronic Health Examination) score can be used as well

Mechanical ventilation: basic objectives of ventilatory support are to maintain comfort, avoid iatrogenesis, and offset physiologic disturbances; the main goals of mechanical ventilation are the removal of carbon dioxide and the oxygenation of tissues; the removal of carbon dioxide is dependent on minute ventilation, which is the product of the respiratory rate and the tidal volume; a change in minute ventilation will result an inverse change in the carbon dioxide level of the same proportion, eg, a 50% increase in minute ventilation will result in a 50% decrease in carbon dioxide (CO_2) on an arterial blood gas (ABG); maintenance of oxygenation is achieved by titrating the fraction of inhaled oxygen (FIO_2) and increasing positive end-expiratory pressure (PEEP); an increase in PEEP will result in an increase in mean airway pressures, which increases oxygenation

Ventilator pressures: peak airway pressure applies when there is airflow in the circuit; it is determined by airway resistance, the size of the endotracheal (ET) tube, presence of an obstruction, bronchospasm, mucous plug, or pneumothorax; plateau pressure applies when there is no airflow in the circuit; it is determined by lung compliance; this is the most important pressure, as it is a reflection of the pressure seen at the alveolar level

Primary modes of ventilation: volume control modes are flow regulated; the practitioner sets tidal volume, rate, PEEP, FIO_2, a flow rate and pattern, and the trigger sensitivity; the inspiratory time (a function of flow and tidal volume) and expiratory (E) time (a function of the rate and inspiratory time), are indirectly set; match flow to the patient's needs and demands; triggers may be flow or pressure; examples of volume control modes are assist-control (AC), synchronized intermittent mandatory ventilation (SIMV), or assist-control/volume control (AC/VC); the main advantage of volume control modes is the ability to tightly control tidal volumes

Pressure control modes: ventilation is pressure regulated; the practitioner sets an inspiratory pressure, inspiratory time, rise time (the time it takes for the ventilator to achieve the set pressure), frequency, PEEP, and FIO_2; expiratory time is set indirectly; volume is variable; tidal volumes change as lung inflammation related to lung compliance changes; examples of pressure-regulated ventilation are pressure control, pressure support, airway pressure release ventilation (APRV), and bilevel; the main advantage is its flexibility to meet patient flow demands and a tendency to be a more comfortable mode of ventilation; the practitioner has direct control over mean airway pressures; the disadvantage is the variability of tidal volume; pressure support ventilation is a common form of pressure-regulated ventilation; there are three main modes — pressure support ventilation, continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP); when you treat a patient with pressure support ventilation, the practitioner sets PEEP or a CPAP level and a pressure support level, which is the level of assistance given with every breath; the practitioner sets trigger sensitivity and the Esense (the ability to cycle the breath off), which is sensed by the ventilator; it is one of the most common modes to encourage patient effort; salvage modes of ventilation (will not be discussed) include APRV, BiLevel, and high-frequency oscillatory ventilation

Weaning off the ventilator: a successful wean is the result of multi-disciplinary care; intensivists should aggressively wean sedation and promote spontaneous breathing; predictors of successful extubation are a negative inspiratory forced volume of -20 cc of water (NIF), a minute ventilation of less than 10 L/min, a respiratory rate

of <30 to 35, and an RSBI <100; RSBI (rapid shallow breathing index; the Tobin index) is a function of the frequency divided by the tidal volume; the most accurate predictor of failure after extubation; its absence is an accurate predictor of successful weaning from mechanical ventilation

Hyperoxia: hyperoxia is harmful in critical illness; recently confirmed in the 2018 IOTA study; in acutely ill adults, liberal oxygen therapy increases mortality without improving other outcomes; supplemental oxygen may be unfavorable above an oxygen saturation range of 94-96%

Assessment of volume status: more invasive monitoring shown not to improve outcomes in ICU; the ProCESS, ARISE, and ProMISe trials concluded that the advanced monitoring requested by early goal-directed therapy using aggressive hemodynamic monitoring did not improve outcomes or mortality in septic patients; physiologic targets (eg, CVP or MAP) have been suggested, but no broadly applicable targets exist for all patients, because they vary based on patient physiology, age, and comorbidities

Arterial line monitoring: most common form of invasive monitoring in the ICU; recommended in Sepsis 3 guidelines; determines beat to beat assessments of systolic pressures; central line monitoring allowing for ScvO2 and central venous pressure measurements should not be used alone to guide fluid resuscitation; since 2008 *Chest* meta-analysis, CVP has fallen out of favor; an isolated CVP value is not very useful, but a trend, especially in setting of a low CVP, may be helpful; SvO2 (oxygen saturation of mixed venous blood) reflects the balance between oxygen consumption and delivery; ScvO2 is not interchangeable with SvO2, which is derived from a pulmonary artery catheter measurement; either can be helpful in septic or cardiogenic shock as a measurement of oxygen delivery; Swan-Ganz catheter has fallen out of favor following 3 major studies

Echo: pulmonary, thoracic, and abdominal ultrasound; the most important type of monitoring in the ICU; it is quick, reproducible, and dynamic, using static and dynamic parameters that should be interpreted differently if the patient is spontaneously breathing or mechanically ventilated; other predictive fluid responsiveness techniques can be used (eg, passive leg raise test, stroke volume variation, pulse pressure variation, IVC (inferior vena cava) collapsibility, arterial waveform analysis, lithium dilution and thoracic bioimpedance)

Shock: 4 different kinds of shock — cardiogenic, obstructive, hypovolemic, and distributive; cardiogenic shock often occurs after ischemia and loss of >40% of LV function; cardiac output is reduced, causing tissue hypoxia and lactic acidosis; stroke volume is reduced; compensatory tachycardia develops, which may further increase myocardial oxygen demand and ischemia, and worsen the infarction

Cardiogenic shock: may occur after acute MI (myocardial infarction), in CHF (congestive heart failure),with arrhythmias, and from toxic ingestion

Obstructive shock: may result from pulmonary embolism, pericardial tamponade, or tension pneumothorax

Hypovolemic shock: can either be hemorrhagic (eg, trauma or GI bleeding) or nonhemorrhagic (eg, burns and diarrhea)

Distributive shock includes septic, anaphylactic, and neurogenic shock; septic shock is a result of infection; anaphylactic shock is uncommon in the ICU, but practitioners should be familiar with anaphylactic treatment, including removing offending agent, establishing airway, restoring circulation, and providing pharmacologic support with epinephrine, antihistamines, and corticosteroids; with neurogenic shock, patients are usually hypotensive and bradycardic; treatment includes fluid and resuscitation for a MAP >65, vasoconstrictor support with norepinephrine or phenylephrine, and inotropic support with dobutamine or epinephrine; atropine can be used for severe bradycardia

Shock treatment: the most important thing is to identify the presence of shock, and then ensure proper resuscitation; the workhorse for this is volume

Ways of expanding intravascular volume: crystalloids — balanced salt solutions vs normal saline; important factor is critically vs not-so-critically ill patient; in the 2018 SALT-ED trial, non-critically ill patients had similar results and outcomes with balanced salt solutions and normal saline; in the 2018 SMART trial, in patients who were severely ill, lower rates of composite outcomes of death from any cause, new renal replacement therapy, or persistent renal dysfunction favored the use of balanced salt solutions; conservative vs liberal crystalloid volume resuscitation also well studied; positive fluid balance and increased CVP are associated with greater mortality; FACTT trial (2006) showed that conservative fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care, without increasing nonpulmonary organ failures

Role of albumin: controversial; a 2011 trial favored albumin in contrast to the 2004 SAFE trial, which suggested no difference between albumin and crystalloid; the 2014 ALBIOS trial found that albumin specifically used in severe sepsis or septic shock did not improve the rate of 1- and 3-month survival; in TBI (traumatic brain injury), albumin is particularly associated with higher mortality rates compared with saline and should be avoided

Other fluids: hydroxyethyl starch has been found to be definitively harmful, leading to greater risk of renal replacement therapy and increased 90-day mortality; role of blood transfusion — less is more; the 1999 TRICC trial showed that a restrictive strategy of red cell transfusion is at least as effective as a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute MI and unstable angina; it improved 28-day mortality, particularly in low APACHE patients and younger patients (transfusion trigger of 7.0); findings confirmed by ABC and CRIT trials; idea that TBI, septic shock, or elderly patients could benefit from more liberal transfusion strategy has not been borne out in trials

Vasopressors: a patient must be adequately resuscitated prior to starting; target MAP is >65; in the 2017 SEPSISPAM trial, investigators compared a MAP of 80 to 85 with a MAP of 65 to 70 in patients with septic shock undergoing resuscitation; the higher MAP goal did not result in significant differences in mortality at 28 or 90 days

Norepinephrine: the first-line pressor in septic shock; has both alpha and beta agonist effects; decreases pulmonary, splanchnic, and cutaneous blood flow, and has some mild cardiovascular effects

Epinephrine: predominantly beta effects, but some alpha effects; increases cardiac output, heart rate, MAP, and coronary blood flow; increases pulmonary vascular resistance (PVR) and right ventricular afterload at higher doses; increases myocardial oxygen demand secondary to tachycardia; increases blood plasma glucose and plasma lactate levels; no mortality difference with norepinephrine or epinephrine, but norepinephrine has fewer side effects; pressor effect is greater at higher doses

Dopamine: increases MAP and cardiac output by increasing heart rate and stroke volume; more arrhythmogenic and tachycardia-inducing than norepinephrine, based on the SOAP II trial (2010); does not enhance renal perfusion (as previously thought)

Vasopressin: reverses a relative deficiency of the hormone; it acts on the V1 receptor; may also improve vascular reactivity to other catecholamines

Dobutamine: a synthetic catecholamine; binds B1 and B2 receptors; a first-line agent to increase cardiac output; it increases myocardial oxygen demand

Milrinone: a PDE3 (phosphodiesterase 3) inhibitor, similar class as caffeine; it increases chronotropy and inotropy, and decreases preload and afterload; it may decrease systemic vascular resistance and lead to hypotension; as a potent pulmonary vascular vasodilator, may be helpful for pulmonary hypertension and right heart failure

Phenylephrine: a selective alpha agonist; primarily provides proximal arterial vasoconstriction and terminal sparing; reflex bradycardia may develop, and it can reduce splanchnic and renal blood flow; it is not ideal for a patient with baseline diminished cardiac output; considered salvage therapy in Sepsis 3 guidelines; however, very common in the ICU, especially in postoperative patients as they emerge from anesthesia; two new pressors are levosimendan and angiotensin II but they are not yet clinically available

Neurological system: of key importance is the approach to the pain and sedation of patients in the ICU; the use of what is recommended to be a care bundle (eg, ABCDE bundle — awakening, breathing, coordinating, delirium recognition, exercise), involve interventions from different providers and have a measurable effect on outcome

Pain: the most valid and reliable pain scales are the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT); vital signs alone should not be used to monitor for pain; a key treatment approach is multimodal therapy; opioids should be first line, even in delirium, to ensure analgesia is appropriate, but should be less preferred over non-narcotic options (eg, gabapentin, epidural, regional anesthesia, acetaminophen/Tylenol)

Sedation: maintenance of high levels are discouraged; the 2008 Wake Up and Breathe trial suggested decreased ICU length of stay and mechanical ventilation duration if patients are not deeply sedated; the Richmond Agitation-Sedation Scale (RASS) and the Sedation Agitation Scale (SAS) are among the most valid and reliable assessment tools; can help reduce the depth of sedation and measure the quality of the sedation; EEG monitoring should be used in patients in whom there is a concern for seizure activity; other agents such as dexmedetomidine and propofol are short-acting and may decrease length of stay and length of mechanical ventilation; spontaneous awakening trials should be recommended in patients who are receiving mechanical ventilation, with daily interruption of sedative drug infusions, causing decreases in duration of mechanical ventilation and length of stay in ICU

Delirium: a major public health problem affecting up to 80% of mechanically ventilated patients; an important predictor of negative outcome; causes increased mortality, length of stay, cost, and long-term cognitive impairment; practitioners should implement delirium prevention strategies such as sleep-wake; the Confusion Assessment Method (ICU-CAM, CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are reliable; benzodiazepines increase the risk of delirium; dexmedetomidine is associated with a lower incidence of delirium, particularly in mechanically ventilated patients; low-dose antipsychotics are not suggested for prevention of delirium; prophylactic Haldol did not reduce mortality at 28 days; early mobilization was associated with improved outcome in a 2009 trial

Seizures: a third of patients in a coma have seizures and up to 20% of these may be nonconvulsive; practitioners should have high level of suspicion and use EEG; status epilepticus is a medical emergency, and studies have suggested a synergistic effect of seizures or status epilepticus in the underlying etiology causing death in the ICU; this is the case in seizures combined with stroke or intracranial hemorrhage; the treatment for seizures is initial intravenous treatment using lorazepam at 0.1 g/kg, and a second line using phenytoin; >60% of these patients will respond after the first dose of treatment

Respiratory system: it is important to identify patients that can breathe spontaneously and wake patients so that they can do so; in the 1995 Spontaneous Breathing Trial, a once-daily trial of spontaneous breathing led to extubation 3 times faster than intermittent ventilation and twice as fast as patients on pressure support ventilation

Acute respiratory distress syndrome (ARDS): using the Berlin classification, there are 3 groups — mild (P/F [PaO_2/FiO_2] ratio <300), moderate (P/F ratio 100-200), and severe (P/F ratio <100); the cornerstone of ARDS treatment is low stretch, established by the 2000 ARDSNet trial of over 800 patients, where mechanical ventilation with a lower tidal volume resulted in a 22% relative reduction in mortality; the optimal level of P power has not been well established; high PEEP and recruitment maneuvers may worsen outcome; other cornerstones of ARDS treatment include neuromuscular blockade and proning; the 2010 ACURASYS trial found that in severe ARDS, early administration of neuromuscular blocking agents improved 90-day survival and increased time off a ventilator without increasing muscle weakness; the PROSEVA trial showed improved mortality in patients that were proned earlier; steroids in ARDS should be avoided, as they may be harmful; ECMO (extracorporeal membrane oxygenation) will not be discussed, but consider early in refractory hypoxemia in ARDS

Pneumonia in ICU: the 2016 IDSA (Infectious Diseases Society of America) guidelines for hospital-acquired and ventilator-acquired pneumonia are an excellent resource; bronchoalveolar lavage is the preferred method for testing, but results between bronchoalveolar lavage and noninvasive testing (eg, ET [endotracheal tube] aspirates) may be equivalent; the duration of antibiotic treatment, antibiotic choice, and clinical outcomes may be the same; in suspected ventilator-associated pneumonia, include coverage for *Staph aureus* and *Pseudomonas*, as well as other Gram-negative bacilli; consider adding a second Gram-negative agent for high-risk patients; know the risk factors for multidrug resistant organisms; the risk of ventilator-associated pneumonia decreases with the length of intubation; the duration of treatment has been established at 7 days for both ventilator- and hospital-associated pneumonia; this shortened duration reduces the risk of recurrent pneumonias due to MDRs (multi-drug resistant organisms); no difference in mortality, recurrent pneumonias, treatment failure, hospital length of stay, or duration of mechanical ventilation; antibiotics should be de-escalated and tailored to specific cultured pathogens; consider MRSA (methicillin-resistant *Staph. aureus*) screening for cessation of vancomycin (nasal MRSA PCR (polymerase chain reaction testing) has a 98% negative predictive value); *Serratia*, *Pseudomonas*, *Acinetobacter*, *Citrobacter*, and *Enterobacter* (ie, SPACE bugs) do not require extended treatment durations per the IDSA guidelines

Noninvasive ventilation: may be underutilized in critical care setting; high-flow nasal cannula may provide some PEEP, which is where benefits may be derived; the 2015 FLORALI trial concluded that high-flow oxygen versus standard oxygen did not result in significantly different intubation rates, but improved 90-day mortality; among extubated patients, when high-flow nasal cannula was used in those at low risk for reintubation, they had a reduced risk of reintubation within 72 hours; in high-risk counterparts, noninvasive ventilation and high-flow nasal cannula resulted in similar reintubation rates and post-extubation respiratory failure; compared with standard nasal cannula treatment, noninvasive positive pressure ventilation resulted in fewer intubations, fewer complications, shorter hospital stays, and lower in-hospital mortality; noninvasive positive pressure is also a cornerstone of treatment for acute hypoxic respiratory failure in immunocompromised patients; early initiation of noninvasive positive pressure ventilation is associated with significant reductions in the rates of endotracheal tube intubation and serious complications (2001 study); in patients with acute cardiogenic pulmonary edema, noninvasive ventilation induces a more rapid improvement in respiratory distress and metabolic disturbances than standard oxygen therapy, but does not affect short-term mortality; older, sicker patients, and those who fail to improve their P/F ratio within the first hour are more likely to fail noninvasive ventilation

Tracheostomy: increases comfort, decreases sedation, increases physical therapy goals, and increases enteral feeding tolerance; timing for tracheostomy does not seem to impact patient ventilator-associated pneumonia, hospital length of stay, admission to long-term care, or 1-year survival

Asthma: hallmarks of treatment include early recognition and administration of therapy, nebulizer MDI (metered dose inhaler) short-acting beta agonists or anticholinergics, oral or parenteral steroids, the maintenance of adequate oxygenation, and monitoring the patient for dynamic hyperinflation or auto-PEEP; the role of noninvasive positive pressure ventilation in asthma was not supported by a 2013 review

Airway emergencies: recognize upper airway emergencies and identify patients quickly; if a first attempt at intubation fails during an upper airway emergency, get help; if you cannot intubate, bag-mask the patient and consider an alternative airway, such as an LMA (laryngeal mask airway); a cricothyroidotomy is the incision of choice for an emergency airway, not a tracheostomy or laryngotomy; place an ET tube or a tracheostomy tube directly into the hole, ideally 6.0 in size

Cardiovascular system: CHF presents a huge medical burden in medical ICUs, and is the primary reason for hospital admission in patients aged 65 or older; a CHF exacerbation is common, and most clinicians are familiar with systolic failure; diastolic failure is primarily an impairment in relaxation of the myocardium; noninvasive ventilation is important in patients with CHF and pulmonary edema; treatment is mostly diuretics administered to 90% of patients by bolus or continuous infusion (same effectiveness); vasodilators with hydralazine or isosorbide dinitrate are often used in therapeutic regimens that include digoxin and diuretics in patients with chronic CHF, and this may have a favorable effect on left ventricular function and mortality; agents that affect the venous system, such as nitrates, are the first-line agents for angina symptoms in MI with CHF, reduce preload, and are desirable because most CHF patients have a high prevalence of CAD (coronary artery disease); arterial agents, such as Nipride (sodium nitroprusside), should be combined with nitrates and hydralazine; ACE inhibitors have been found to reduce total mortality and hospitalization in a broad range of CHF patients; beta-blockers can worsen CHF acutely

Acute coronary syndromes: patients more significantly benefit from fibrinolytic therapy during the golden 1-2 hours after presentation; the MONA algorithm (M — morphine, O — oxygen, N — nitroglycerin sublingual, A — aspirin as chewed by the patient) should be initiated in most cases; clopidogrel upfront with a loading dose should be used for patients who may be CABG (coronary artery bypass graft) candidates or as an outpatient regimen; should be continued for 12 months, but recent data suggest using it beyond a year; heparin is the best choice vs others such as low-molecular-weight heparins; beta blockers and high-dose statins should be considered early and after discharge; aspirin (dose unimportant) should be used in STEMIs (ST-elevation Mis) and NSTEMIs (non-ST elevation MIs); ACE inhibitors should be used if left ventricular function is depressed; a door-to-balloon time of 90 minutes or less is recommended for percutaneous coronary interventions in STEMIs; in the post-arrest (any cause) patient, consider use of cooling or targeted temperature management early to improve neurological outcomes

Arrhythmias: in bradyarrhythmias, there should be a low threshold for using pacing in a transcutaneous or

transvenous approach in the ICU; for supraventricular tachycardias, use adenosine, beta-blockers, calcium channel blockers, and cardioversion

Atrial fibrillation: treatment is divided into rate control and rhythm control; rate control is often the easiest goal, using diltiazem with a loading dose, esmolol, or amiodarone; it can be followed by an oral regimen of beta blocker (preferably metoprolol) or diltiazem; rhythm control can be obtained with amiodarone or sotalol, but most often is obtained with external synchronized cardioversion (administer sedation and use a synchronized approach of 50 to 100 Joules to start); ACLS (advanced cardiac life support) algorithms give more details on sequential treatment of various arrhythmias

Hypertensive crises: the main goal is to stop and reverse end-organ damage, maintaining organ perfusion, and avoiding complications; a lowering of the MAP by 20%, or maintaining a MAP between 100 and 110 is optimal; use nitroprusside, nitroglycerin, labetalol, and nicardipine; targeting <180 versus <140 mm Hg has no outcome effect in those with intracranial hemorrhage

Renal system: the prevalence of AKI (acute kidney injury) in ICUs is about 6%; two-thirds of these patients will require renal replacement therapy, of whom 50% will die; independent risk factors for hospital mortality include use of vasopressors, mechanical ventilation, septic shock, cardiogenic shock, and hepatorenal syndrome; postoperative cardiac patients with AKI have an ICU length of stay that is twice as long, and a mortality that is around 20%, compared with patients with normal renal function; creatinine generation falls as ICU length of stay increases, making it an imperfect marker; other markers of kidney injury are not yet used in the clinical setting; administration of diuretics (ie, the Lasix challenge), is performed; high-dose furosemide helps maintain urinary output, but does not impact survival or renal recovery rate; there is no difference in mortality, number of dialysis sessions, or time on dialysis; a meta-analysis of 9 studies with 549 patients found no reductions in hospital mortality, need for dialysis, or persistent oliguria; there is an increased risk of temporary deafness and tinnitus; diuretics do not change outcomes

Renal replacement therapy: criteria for dialysis; there are no specific BUN or creatinine levels that would require the practitioner to order dialysis; remember the AEIOU mnemonic (A — acidosis, E — electrolyte abnormalities, I — intoxication, O — intractable volume overload, U — uremia); when to initiate therapy? the 2016 AKIKI trial and the 2016 ELAIN trial are conflicting and cannot determine if there is a benefit to early initiate of therapy; in a Cochrane Review, CRRT (continuous renal replacement therapy) was shown to achieve better hemodynamic parameters, such as MAP, than IHD (intermittent hemodialysis) which is why CRRT is the modality of choice in the ICU

Gastrointestinal system: an often-overlooked aspect of critical care is nutritional therapy; the Van den Berghe trials and the NICE-SUGAR trial confirmed that mortality exists among adults in the ICU if their glucose levels are too high or too low; the final recommendation is to target a level between 150 and 180; ICU providers should be familiar with the ASPEN nutritional guidelines (most recent version published 2016); specific recommendations in adults include initiating early enteral nutrition therapy within 24 to 48 hours after admission; do not wait for overt signs of bowel function, such as flatus or low residuals; use high-dose protein initially with gastric feeds; post-pyloric tube placement to prevent aspiration not mandatory; do not use residuals to guide enteral feeding; consider use of prokinetics in patients with high risk for aspiration; do not stop enteral feeds for diarrhea; maintain feeds during procedures and travel; consider adding fiber to regimens; usefulness of probiotics and glutamine in ICU has not been established; if only TPN (total parenteral nutrition) can be used, it should be held until 7 days for low-risk patients, but immediately used in severely malnourished patients; adding TPN to oral or enteric tube diets recommended if GI modalities cannot provide 60% of daily caloric requirements, usually after 7-10 days; use fluid-restricted, energy-dense formulas for acutely injured patients; use standard enteral formulas for renal failure patients unless they have electrolyte abnormalities; use an increased amount of protein for patients on CRRT; CALORIES trial (2013) compared enteral vs parenteral nutrition found no difference in 30-day mortality

Antibiotics in ICU: delays in appropriate antibiotic therapy increase mortality; administration of antibiotics within the first hour of documented hypotension improves outcomes; more rapid completion of a 3-hour bundle of sepsis care and rapid administration of antibiotics was associated with lower mortality in a 2017 study; a 2006 study revealed that the median time to effective antibiotics was 6 hours, which is much too late; appropriate antibiotic use within the first hour was associated with a 79.9% survival; survival decreased by 7.6% for every hour over the first 6 hours that antibiotics were delayed; important to coordinate with eg, interventional radiology and surgery for prompt source control; the STOP-IT trial helps guide antibiotic therapy for patients with intra-abdominal infections; patients with an adequate source control procedure had similar outcomes after a 4-day antibiotic treatment regimen compared with a longer treatment regimen

Antifungal therapy: consider adding for persistent fevers or septic shock with neutropenia; consider in patients with extended ICU stay, renal failure, mechanical ventilation, parenteral nutrition, recent abdominal surgeries, or immunosuppression

Steroids and sepsis: in the CORTICUS trial (2008), hydrocortisone did not improve survival or reversal of shock in patients with septic shock; the ADRENAL trial (2018) found that among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not lead to a lower 90-day mortality versus placebo

Toxicology: resuscitation, stabilization, diagnosis, and specific antidotes or interventions should be administered in a time-sensitive manner; GI decontamination involving emesis-inducing agents is not recommended; gastric lavage, cathartics, and activated charcoal may be used in certain cases; vital signs and level of consciousness are important and may point towards the offending agent and the route of decontamination; toxin elimination is important (eg, acetaminophen overdoses), using antidotes such as N-acetylcysteine, which is most

effective within 8 hours and needs continuous evaluation of liver function before completion of N-acetylcysteine treatment

Ethylene glycol and methanol: evaluation is mostly of the CNS, gastrointestinal, and cardiopulmonary systems, identifying anion gap metabolic acidosis as well as an osmolar gap; fomepizole and dialysis are the treatments of choice; flumazenil is the reversal agent for benzodiazepines; tricyclic antidepressants have no reversal agents and involve charcoal use, consideration of gastric lavage, and airway and cardiac monitoring; intubation may be needed; blood alkalinization is recommended; in refractory cases, hypertonic saline and lipid infusions are used

Other toxins: narcotic overdoses not as life threatening as benzodiazepine and alcohol overdoses; an antidote (naloxone) can be given by multiple routes; the cholinergic syndrome with organophosphate, toxidromes or carbamates, and nerve gas have the SLUDGE manifestation (S — salivation, L — lacrimation, U — urination, D — defecation, G — gastric upset, E — emesis); treat with atropine and pralidoxime

Cyanide toxicity: treat with hydroxocobalamin; sodium thiosulfate regimens are no longer available; carbon monoxide poisoning is treated with hyperbaric oxygen

Impacts of critical care illness: an important emerging field of research; the 2013 BRAIN-ICU study found that patients in medical and surgical ICUs are at high risk for long-term cognitive impairment; longer duration of delirium in the hospital was associated with worse global cognition and executive function scores at both 3 and 12 months; post-intensive care (PIC) syndrome is defined as a new or worsening impairment in physical (eg, ICU-acquired neuromuscular weakness), cognitive (eg, thinking and judgment), or mental health status arising after critical illness and persisting beyond discharge from the acute care setting; PIC syndrome has been identified as a condition that warrants awareness as patients are discharged from the ICU

Suggested Reading

Esteban A et al: A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med* 1995 Feb;332(6):S1390-345-50; **Kalil AC et al:** Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016 Sept;63(6):e61-111; **Semler MW, et al:** Balanced crystalloids versus saline in critically ill adults. *N Engl J Med* 2018 Mar;378(9):829-39.

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Common Sleep Disorders

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Sleep disordered breathing: conditions that involve breathing disorders during sleep (obstructive sleep apnea [OSA], central apnea, upper airway resistance syndrome, and hypoventilation)

OSA: characterized by repetitive cycles of upper airway obstruction; complete cessation of breathing is apnea; shallow breathing is hypopnea; sleep fragmented by cyclical intermittent hypoxemia that leads to many health consequences; disorders quite prevalent, but depend on what metrics used and distribution of risk factors in population being studied

- Prevalence: estimated prevalence in North America is 20% to 30% in males, 10% to 15% in females when broadly defined as an apnea-hypopnea index greater than 5 events per hour, as measured by a polysomnogram; apnea-hypopnea index is a count of number of apneas and hypopneas that occur in 1 h; greater than 5 events is abnormal; 24% of people over 65 years have OSA; 46% of those with OSA have moderate to severe sleep apnea; up to 50% of nursing home residents have clinically significant sleep apnea; up to 50% percent of patients with asymptomatic or mildly symptomatic heart failure have sleep disordered breathing (eg, Cheyne-Stokes respiration, central sleep apnea, or OSA)
- Pathophysiology: any factor that alters upper airway (nasopharynx, hypopharynx, oropharynx) patency; determined by activity of upper airway muscles, cranial and soft tissue structures, and sleep state; rapid eye movement (REM) sleep (ie, dream stage of sleep) characterized by physiologic atonia with most muscles paralyzed so person does not act out dreams; upper airway is most narrow during REM sleep; in supine sleep, gravity no longer keeps upper airway patent and tongue can fall back and further narrow upper airway to increase apneic and hypopneic episodes; in normal non-REM sleep, there is physiologically reduced tonic input to upper airway muscles, diminished reflexes that protect the pharynx from collapse, and increased chemoreceptor pC02 set point; in certain people, these conditions increase sensitivity to hypocapnia and lead to apnea; factors are interactive; sleep is associated with pharyngeal narrowing and substantial increase in inspiratory resistance, even in normal individuals; if someone has anatomically abnormal pharynx in REM sleep or supine sleep, narrowing in upper airway may be increased and partial collapse results in snoring and hypopneas, with possible prolonged obstructive hypoventilation; complete closure of upper airway for a few seconds is apnea; most important consequences are increased cardiovascular risks (eg, hypertension, myocardial infarction, atrial fibrillation, and cerebrovascular disease/stroke); there is increased mortality with severe sleep disordered breathing and OSA (shown in several epidemiologic studies); association with metabolic syndrome and type 2 diabetes; daytime sleepiness may lead to increased car accidents; associated with non-alcoholic fatty liver; neuropsychiatric consequences of OSA include depression, anxiety, impaired cognition, difficulty concentrating, difficulty learning new things, decreased alertness, and difficulty in memory formation; associated with gastroesophageal reflux disease, nocturia, pregnancy complications, erectile dysfunction, and decreased libido
- Signs and symptoms: most with OSA present with classical clinical feature of excessive daytime sleepiness; severity measured by Epworth Sleepiness Scale; score does not necessarily correlate with severity of OSA; fragmented sleep and repeated awakening due to respiratory events may be reported by patient as waking up gasping or choking (may have witnessed apneas); bed partner may complain of loud snoring, which may also wake the patient
- Risk factors: those that reduce upper airway size or predispose to upper airway collapse; obesity; male sex; post-menopausal women; craniofacial abnormalities (retrognathia — receding chin, micrognathia — small chin, brachycephaly — small head); soft tissue abnormalities (large uvula, tonsillar enlargement [especially in children with OSA], macroglossia [big tongue], or long soft palate); predispose to narrowed upper airway, which can lead to OSA during sleep; alcohol and sedatives aggravate but do not cause OSA
- Epworth Sleepiness Scale: several items; patients rate chance of dozing off under specific circumstances; scores range from 0 to 3 for each item; eg, what are the chances of dozing off when you are sitting and reading (0 never, 1 slight chance, 2 moderate chance, 3 high chance)? while watching TV? sitting inactive in a public place? as a passenger in a car for 1 h? while sitting and talking to someone? while lying down in afternoon if circumstances permit? while sitting quietly after lunch without alcohol? as driver of a car while stopped for a few minutes in traffic or at red light or stop sign? sum scores (range, 0 to 24); higher score indicates higher likelihood of daytime hypersomnolence; cutoff of 10 indicates daytime hypersomnolence; certain items more important than others (eg, moderate chance of dozing while sitting and talking or as a driver stopped for a

few seconds at a red light or stop sign); questionnaire not specific for OSA; subjective measure of daytime sleepiness

- Differential diagnosis of excessive daytime sleepiness: OSA, narcolepsy, upper airway resistance syndrome, long sleep syndrome, periodic limb movements during sleep, neurologic disorders (eg, Parkinsonism), delayed sleep phase syndrome; most common is insufficient sleep syndrome (adults need 7 to 9 h sleep; most do not get that nightly)
- STOP-BANG questionnaire: developed initially for preoperative clinic screening to determine OSA risk; 8 items; whether person's snoring is very loud? how tired person feels? how fatigued? do they have daytime sleepiness? have there been any observed apneas? is blood pressure elevated? increased risk with BMI greater than 35 kg/m^2, age over 50, neck circumference greater than 40 cm, male; if 3 or more "yes" responses, high risk of OSA and diagnostic testing recommended
- Physical examination: may guide treatment decisions; physical exam classically shows obese person with hypertension who may have fallen asleep in waiting room; upper airway with tonsillar enlargement; nasal inspection for polyps or obstruction, deviated septum; soft palate to look for elongated uvula; lateral side of face for retrognathia; large tongue (macroglossia), other facial abnormalities; neck size greater than 17 inches in men and greater than 16 inches in women; increased soft tissue around neck may narrow the upper airway; formal ENT evaluation indicated for patients who may have factors amenable to surgical treatment
- Sleep study for definitive diagnosis
  - In-lab polysomnography: is gold standard; many EEG (electroencephalogram) leads used to determine sleep state; EMG (electromyogram) used to evaluate for limb movements and identify REM sleep; microphone for snoring; nasal and oral airflow measurements; thoracic and abdominal respiratory effort measurements; pulse oximetry
  - Home sleep study: quality varies; to be adequate, needs to measure pulse oximetry, nasal or oral airflow, and thoracic and abdominal respiratory effort to determine apnea and hypopnea episodes; most do not have EEG lead so cannot determine sleep stage; difficult to evaluate central sleep apnea, especially if abdominal and thoracic belts not used; can be used for patients at moderate to high risk for OSA who do not have other comorbidities (no heart failure or chronic respiratory failure that would require better observation, no neurologic disorders such as stroke, no need to evaluate other events such as leg movements, periodic limb movements of sleep [PLMS], or seizures, no suspicion of REM behavior disorder [movement instead of muscle paralysis during REM sleep allows patients to act out their dreams])
  - Scoring criteria: for OSA, central apnea, mixed apnea, and hypopnea; respiratory event identified by cessation or reduction of airflow lasting 10 seconds or longer; events usually associated with arousals on EEG; for obstructive apnea, no airflow for greater than 10 seconds plus increasing respiratory effort to break out of apneic episode; for hypopnea, reduced airflow to 30% of baseline plus desaturation or EEG arousal; for mixed apnea, complete absence of nasal and oral airflow with absent respiratory effort followed by gradual increased effort that eventually breaks apnea (central apnea with absent respiratory effort followed by conversion to obstructive apnea); mixed apnea treated as respiratory event for apnea-hypopnea index; uncertain whether mixed apnea itself has major implications or special implications in terms of consequences of sleep apnea; important to distinguish central apnea from obstructive apnea; central apnea has absence of airflow at nose and mouth for ≥10 seconds but complete absence of respiratory effort in thoracic or abdominal belt because no signal from brain for breathing (apnea and no respiratory effort); to diagnose OSA, apnea-hypopnea index greater than 5 in patients with 1 or more symptoms (sleepiness, non-refreshed or non-restorative sleep, fatigue, or insomnia symptoms); patient may report waking up with breath holding, gasping or choking, habitual snoring, or their partner recalls episodes of stopped breathing and is worried about them; patient may have consequences of sleep apnea (hypertension, cognitive dysfunction, memory problems, difficulty concentrating, mood disorder, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes); apnea-hypopnea index of 5 or more episodes per hour with symptoms or consequences of OSA is diagnostic; apnea-hypopnea index of ≥15 episodes per hour regardless of symptoms or comorbidities also diagnostic of OSA
- Treatment: if the person is obese, diet and behavior modification should be recommended; surgical treatments for obesity should be recommended in some cases; these are not immediate fixes for OSA, as lifestyle modification takes a lifetime
  - Positional therapy: for those who develop respiratory events while in supine position with few apnea or hypopnea episodes on their sides; a ping pong ball or tennis ball can be sewed into the back of the neck on the pajama top; specialized pillows are available that act as belts; the pillow is tied around the thorax in the front, and the back has a bulge; patient prevented from becoming completely supine because it is uncomfortable to lie on back; patient will immediately turn to side while sleeping; unfortunately, many patients do not have events confined to certain position; these patients require other forms of therapy
  - Medications: past attempts to increase muscle tone with medications; presently, there are no medications available to increase upper airway muscle tone
  - Hypoglossal nerve stimulation: new, FDA-approved device; implantable; for patients who have failed continuous positive airway pressure (CPAP) treatment, have BMI <32; must undergo drug-induced sleep endoscopy to rule out other forms of collapse; endoscopy and device implantation by ENT surgeon
  - Nasal continuous positive airway pressure (CPAP): is gold standard treatment for OSA; mechanically stents upper airway; bi-level positive airway pressure therapy also available; automated CPAP has internal algorithm to detect when apneas and hypopneas occur and increase pressure as needed; nasal CPAP improves quality of life and sleep quality and reduces daytime hypersomnolence; adherence less than optimal with up to 30% not using CPAP over long term;

complaints about mask discomfort, nasal discomfort, nasal congestion, dry nose, dry red eyes, background machine noise, ear pain, headache; may forget to use or pull mask off during the night because of sensations of claustrophobia; important to follow up CPAP prescription with patient during first week to ensure adequate use and comfort and to troubleshoot

Other treatments: oral appliance fitted by a specialty dentist can be used to pull out tongue during sleep to increase the space of the upper airway; ENT surgeon can evaluate patients for surgery on soft tissue of the nose, correct deviated septum, remove nasal polyps, alter chin position, cut off uvula; surgical options limited because upper airway narrowing may not be limited to 1 location, so patient may be left with residual OSA that still requires CPAP; tracheostomy is therapy of last resort, bypassing upper airway; many impacts on quality of life

Central sleep apnea: repetitive cycles of cessation of breathing with loss of ventilatory effort during sleep; primary (idiopathic central sleep apnea) or secondary (Cheyne-Stokes breathing); Cheyne-Stokes breathing characterized by central apneas occurring during decrescendo portion of cyclic crescendo-decrescendo respiratory pattern; often seen in patients with stroke and heart failure; breathing pattern is crescendo, decrescendo, apnea; secondary central apneas can be associated with medical conditions (acromegaly, renal failure), drugs (chronic opioid use or opioid abuse), and during high altitude periodic breathing; alternatively, central sleep apnea can be categorized pathophysiologically as hyperventilation-related central sleep apnea or hypoventilation-related central sleep apnea; hyperventilation-related central sleep apnea has Cheyne-Stokes breathing (seen in stroke and heart failure); hypoventilation-related central sleep apnea has alveolar hypoventilation that occurs during day and worsens at night; seen with opioid abuse, severe neuromuscular disease like post-polio syndrome, central nervous system disorder like encephalitis, severe pulmonary mechanical abnormalities due to kyphosis

Treatment: complicated; a lot of research ongoing; treat underlying condition (stroke, heart failure); stop medications that could be respiratory suppressants; for the hyperventilation-associated central sleep apnea, CPAP may be effective if patient symptomatic with moderate to severe central sleep apnea; if patient with heart failure has a preserved ejection fraction greater than 45% and has moderate to severe central sleep apnea, a type of positive airway pressure called Adaptive Servo Ventilation (ASV) is an option; in patients with ejection fraction less than 45%, provide supplemental oxygen and treat heart failure

Chronic insomnia: insomnia symptoms occurring at least 3 times per week and persisting for at least 3 months; most patients report years of symptoms; patients may recall an initial stressful event that triggered insomnia, but trigger does not have to be present to diagnose; often night-to-night variability with waxing and waning course related to psychosocial stressors or medical or psychiatric comorbidities; history shows that patient may report difficulty falling asleep, difficulty staying asleep, or early morning awakening; sleep history needed to differentiate; to be considered a disorder, there has to be impaired daytime functioning; ask about comorbidities (psychiatric or medical), medication use (over-the-counter or prescribed opioids or antidepressants) that could precipitate or perpetuate; check for presence of other sleep disorders, eg, OSA or restless leg syndrome; most adults fall asleep within 10 to 20 minutes of attempting to sleep and spend less than 30 minutes awake during night; in sleep onset insomnia, 1 to several hours may be required to fall asleep; some may have no problem falling asleep but wake up in the middle of the night and take longer than 30 minutes to fall back to sleep; early morning insomnia is termination of sleep at least 30 minutes prior to desired wake up time; impaired daytime functioning should be assessed; does patient feel fatigue or malaise during day? do they report poor attention or concentration? has their social, educational, or vocational life been impacted (eg, student with difficulty concentrating in class or grades are slipping)? mood disturbance or irritability because of lack of sleep? daytime sleepiness? reduced motivation or energy (person no longer participates in activities they used to enjoy)? increased errors? involved in an accident because of impaired daytime functioning? behavioral problems associated or reported by others (hyperactivity, impulsivity, or aggression)? in children, sleep disordered breathing and insomnia causing excessive daytime sleepiness may manifest as hyperactivity or impulsivity; ongoing worry about sleep? do they feel something bad is going to happen because they are not sleeping as they should? obtain detailed sleep history and ask patient to maintain sleep diary for 2-week period; forms are available online or ask patient to record when they go to bed, when they think they fell asleep, how many times they think they wake in the night, how long to fall asleep after awaking in the night, when they wake up for the day, how many naps they take during day, what their sleep environment is like (is it a calming, quiet, dark, cool room?), distractions? stressors that may be triggering or perpetuating insomnia symptoms? do they have a bed partner? pets that sleep with them (dog or cat that jumps onto the bed or moves around and prevents them from falling asleep when they wake up in the middle of the night)? all of these can contribute to insomnia symptoms; ask about depression and anxiety, which are consequences and triggers for insomnia; medication history (including over-the-counter and when they take medication in relation to time they want to fall asleep); what patient is doing 1 hour or so prior to sleep is important (media, TV, electronics); not always necessary to perform polysomnography when evaluating insomnia unless risk factors for OSA are present

Actigraphy: objectively examined sleep; wrist watch that patient wears for several nights to show pattern of when they fall asleep, how often they wake up in night, when they wake up in morning; measures movement; has light and dark sensor to get rough estimate of sleep onset; difficult to assess sleep and wake times if patient moves a lot throughout night; based on presumption that when there is minimum movement, sleep is occurring

Treatment: patience and lifestyle modification; identify and address precipitating and perpetuating factors; mainstay is cognitive behavioral therapy (CBT) and short-term pharmacotherapy; studies show that combination CBT plus pharmacotherapy or CBT alone is far better than

pharmacotherapy; if patient, despite identifying and addressing their precipitating and perpetuating factors, continues to exhibit insomnia symptoms, CBT should be considered; referral to psychologist, psychiatrist, or sleep physician who engages in CBT very important; apps available to assist patient with CBT

Cognitive behavioral therapy: behavioral aspect involves sleep hygiene education, stimulus control, relaxation, and sleep restriction therapy; cognitive aspect involves teaching patient importance of sleep, examining patient's worries about concept of sleep and other anxieties and stressors; patients become concerned that they will not be able to perform the next day or they will perform poorly; this worry can exacerbate their difficulty falling asleep and create a vicious cycle; cognitive therapy needs to address this negative cycle; sleep hygiene is teaching patient to improve and maintain good sleep (eg, bedroom should be place for sleep, not work or computer or texting or TV); 1 hour before sleep should be wind-down time to put aside electronics and try relaxation techniques (listening to mellow music, reading an old fashioned, boring book, flipping through a magazine in dim light); avoid smoking or other nicotine products during evening; avoid caffeinated beverages after lunch; avoid alcohol near bedtime, late afternoon, or evening; regular exercise for at least 20 minutes, but preferably more than 4 to 5 hours prior to bedtime; avoid daytime naps, especially those that are longer than 20 to 30 minutes; maintain regular sleep schedule on weekdays and weekends; over several sessions, the patient can be taught and reminded of what good sleep hygiene is

Sleep restriction: most adults need 7 to 9 hours of sleep; initially, set wake up time to that best-suited to patient lifestyle and allow 5 to 6 (maximum 7) hours of sleep; calculate bedtime accordingly; most people with insomnia go to bed very early in hopes of falling asleep, but become frustrated when they cannot

Medications: benzodiazepines, non-benzodiazepine hypnotics, melatonin agonists, antidepressants (Doxepin), and orexin receptor antagonist; potential benefits of pharmacologic therapy in sleep quality and daytime function needs to be balanced against risk of side effects and physical and psychologic addiction that can occur with long-term use; important to look at clinical setting in which these medications prescribed and patient comorbidities; increased risk of medications in patients who are pregnant, consume alcohol, have hepatic or renal disease, have age greater than 75, significant pulmonary disease or comorbid sleep apnea; all sleep medications have a respiratory suppressant effect and may worsen sleep apnea or breathing during sleep; if pharmacotherapy used, physician should become familiar with 1 medication from each class and become familiar with sides effects and half-life; medication should only be used for short term, especially if patient has moderate to severe insomnia and they are anxious about consequences of insomnia and daytime functioning; should use CBT instead as primary treatment; for sleep onset insomnia, short-acting medication may be reasonable, as they produce less residual somnolence the following morning (drugs with durations less than 8 hours include zaleplon, zolpidem, triazolam, lorazepam and ramelteon); for sleep maintenance insomnia, a longer-acting medication may be chosen (extended-release zolpidem) but patients should be warned that they may be quite drowsy with hangover effect the next morning; for awakening in the middle of the night, zaleplon and sublingual zolpidem have been developed for use during night as long as patient should have at least 4 hours of time remaining in bed after administration because of residual impact on morning functioning

Circadian rhythm disorders: delayed sleep phase syndrome and advanced sleep-wake phase disorder; both may present as insomnia; need good clinical history to differentiate

Delayed sleep-wake phase disorder: circadian system promotes wakefulness until late in evening; person may not go to bed until after midnight (or 3:00 or 4:00 AM); if sleep attempted at an earlier or socially acceptable time, the patient will complain about sleep onset insomnia (hard time falling asleep); they cannot fall asleep earlier (at 10:00 or 11:00 PM); if the patient has no morning obligations and are left undisturbed (weekends or on vacation), may sleep until noon or much later and then function quite well without complaints; however, when they have conventional rise times like 6:00 or 7:00 or 8:00 AM to get to school, work, or some other function, patients have great difficulty waking up and feeling alert; may complain about daytime hypersomnolence; presentation similar to insomnia and sleep disordered breathing; sometimes seen in adolescents and young adults; may only become problem because they have hard time keeping up with their school work or they have just started a job and have work requirements; oftentimes, college students who have this condition delay their first class of the day until afternoon and avoid morning classes — they change their lifestyle to fit their circadian rhythm disorder

Advanced sleep-wake phase disorder: characterized by patient wanting to sleep earlier in the evening than what is conventionally acceptable (6:00 or 7:00 PM) and then they wake up early in the morning and cannot get back to sleep; patient may complain of difficulty maintaining sleep or early morning awakening; can be seen among elderly and as age progresses

Treatment: refer to a sleep physician; involves use of melatonin and light therapy to shift the circadian rhythm appropriately

Restless leg syndrome (RLS): characterized by unpleasant or uncomfortable urge to move legs that occurs during periods of inactivity (particularly evenings) and is transiently relieved by movement; patient may say that they have a pins and needles sensation in their legs or pain in legs when trying to fall asleep or while lying down quietly; sensation only improved and relieved when they move their legs; may interfere with ability to fall asleep, so patient may complain of sleep onset insomnia; during sleep, most patients have periodic limb movements of sleep (PLMS), which may or may not be associated with arousal from sleep; most cases idiopathic; risk factors include family history, iron deficiency, uremia, neuropathy, diabetic neuropathy, alcoholic neuropathy, spinal cord injury (often have involuntary twitches of legs), pregnancy, Parkinson disease

Treatment: address underlying condition; identify and treat iron deficiency to a fasting serum ferritin level of less than or equal to 75 mcg/L; pharmacologic therapy for severe persistent RLS with dopamine agonist (pramipexole or ropinirole) or alpha-2/delta calcium channel ligand (gabapentin), particularly if patient has painful peripheral neuropathy (diabetic neuropathy)

Suggested Reading

Abbott SM et al: Circadian rhythm sleep-wake disorders. Psychiatr Clin North Am 2015 Dec;38(4):805-23; **Jaffe F et al:** Sleep-disordered breathing in depression and schizophrenia. *Psychiatry (Edgmont)* 2006 Jul;3(7):62-8; **National Sleep Foundation:** Sleep Diary. https://www.sleepfoundation.org/sites/default/files/SleepDiaryv6.pdf. Accessed November 19, 2018; **Venkateshiah SB et al:** Restless legs syndrome. Crit Care Clin 2015 Jul;31(3):459-72.

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Altitude Illness

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History: long been recognized that high altitude can impact health; as early as 30 BC, Chinese history refers to Great Headache Mountain and Little Headache Mountain, warning about dangers of traveling to high altitudes in parts of present-day Afghanistan; 1590, Jesuit priest Joseph de Acosta published account of acute mountain sickness in Andes mountains; 1924, British Mount Everest expedition made 3 summit attempts on Mount Everest; second attempt, Edward Norton ascended to 28,130 feet without supplementary oxygen; first successful summit of Mount Everest credited to Edmund Hillary and his Nepalese Sherpa, Tenzing Norgay, reached summit in 1953 with supplementary oxygen; 1978, Reinhold Messner and Peter Habeler made first ascent of Mount Everest without supplementary oxygen

Background: travel and enjoying mountains more common with tourists than with extreme mountain climbers; in 2016, 86 million visitors traveled to Colorado, >20 million of whom went to ski resorts; knowledge about how altitude affects health essential for physicians, not only in Colorado but for any physician caring for individuals who wish to visit mountains

Definitions: high altitude variably defined; in general, moderate altitude 5000-10,000 feet; high altitude 10,000-14,000 feet; very high altitude 14,000-18,000 feet; extreme altitude 18,000-29,028 feet (summit of Mount Everest)

Pathophysiology of ascending elevation: barometric pressure decreases logarithmically as altitude rises; varies somewhat with latitude and season of year but estimated at 760 mm Hg at sea level and 253 mm Hg Mount Everest summit; partial pressure of oxygen (PO_2) decreases as altitude increases although remains constant 21% of barometric pressure; eg, at ski resort, elevation of 10 000 feet, inspired PO_2 only 70% of value at sea level; summit of Mount Everest, inspired PO_2 <30% of value at sea level; as a consequence of decreased inspired PO_2, alveolar PO_2, arterial PO_2, and oxygen saturation tend to decrease with progressive elevation; body's response to these changes is to protect alveolar PO_2 and arterial oxygen saturation as well as hemoglobin concentration in order to maintain oxygen delivery to tissues; nearly every organ system affected by high altitude

Acclimatization: reason some can tolerate high altitude while others cannot; hyperventilation most important feature of this adaptation; hypoxia stimulates peripheral chemo-receptors, primarily carotid bodies, which then trigger hyperventilation; American Medical Research Expedition (AMRE) to Mount Everest in 1981 led by John West was first study to take physiologic measurements at summit; found that subjects able to increase minute ventilation 5-fold compared with sea level, effectively decreasing partial pressure of carbon dioxide (PCO_2) to 7.5 mm Hg and increasing pH to 7.7; based on alveolar gas equation, this increases alveolar PO_2 to approximately 35 mm Hg at summit; based on these values, estimated that arterial PO_2 28 mm Hg; although much lower than arterial PO_2 of 95 mm Hg at sea level, alveolar PO_2 at summit might be just enough to permit ascent without supplemental oxygen; fully acclimatized individuals able to hyperventilate better than acutely exposed individuals; respiratory alkalosis induced by hypoxic ventilatory response tends to inhibit ventilation via central and peripheral chemoreceptors; with acclimatization, bicarbonate moves out of cerebrospinal fluid (CSF) to normalize CSF pH and kidneys excrete bicarbonate to normalize arterial pH; greater ventilation is therefore possible at lower levels of CO_2; hypoxemia also results in increased 2,3-diphosphoglycerate (2,3-DPG), resulting in rightward shift of oxyhemoglobin dissociation curve, favoring release of oxygen from blood to tissues; this is counteracted by leftward shift of curve caused by respiratory alkalosis of hyperventilation; result is increase in oxyhemoglobin in lungs which raises oxygen saturation; in theory this facilitates oxygen unloading in tissues; studies have found that hemoglobin P_{50} (HbP_{50}), ie, arterial PO_2 at which 50% of hemoglobin is saturated, is stable at roughly 27 mm Hg throughout elevations tested due to opposing effect of alkalosis shifting the curve to the left; hemoglobin concentration also contributes to arterial oxygen content; hemoglobin concentration rises acutely due to high altitude diuresis and hemoconcentration; erythropoietin (EPO) production increases at 24-48 hours, which leads to increased red blood cell production; long term, red blood cell mass and plasma volume rise in tandem, causing hemoglobin concentration to level out at 6 weeks at a given altitude; 2009, study published in *New England Journal of Medicine* by Caudwell Xtreme Everest Research Group expanded on results of AMRE study; reported on additional arterial blood gas studies and oxygen content in 10 subjects ascending Mount Everest for medical research expedition; acclimatization process and ascent took approximately 80 days; study demonstrated that with increasing altitude, partial pressure of arterial oxygen (PaO_2) steadily decreases; arterial oxygen saturation relatively well maintained due to properties of oxyhemoglobin dissociation curve; hemoglobin concentration increases from roughly 15 mg/dL to roughly 20 mg/dL; as a result, arterial oxygen content well preserved until about 23,400 feet; acute hypoxia

also activates sympathetic nervous system leading to tachycardia; resting heart rate progressively increases with altitude, returning to baseline with return to sea level; with acute hypoxia, cardiac output increases proportionately to heart rate while stroke volume remains relatively constant; within a few weeks of acclimatization at altitude, cardiac output for a given level of work approaches that at sea level; because heart rate typically remains elevated, this suggests that stroke volume falls; echocardiographic studies have shown that myocardial contractility is maintained, meaning that reduction in stroke volume likely due to decrease in plasma volume; also increase in systemic blood pressure over first 7-10 days at altitude, so patients with hypertension recommended to assess blood pressure when traveling to higher elevations; in pulmonary circulation, altitude also leads to hypoxic pulmonary vasoconstriction; normally, this mechanism improves ventilation/perfusion (V/Q) mismatch, but value at altitude in setting of underlying normal lung parenchyma unclear; pulmonary capillary wedge pressure remained ≤12 mm Hg and right atrial pressure ≤5 mm Hg; at tissue level, over time, increase in capillary production due to vascular endothelial growth factor (VEGF) and increase in red blood cell production due to EPO as well as an increase in mitochondrial energetics; thus, acclimatization a complex process that begins within seconds of arriving to altitude and continues for weeks, months, and even years

Acute mountain sickness (AMS): generally occurs at elevation >8000 feet but can develop as low as 6500 feet; studies conducted in tourist populations in early 1990s estimated incidence of AMS 25% at elevations of 6300-9700 feet and 42% at elevations >10,000 feet in Colorado; early 1990s, scoring system for AMS, Lake Louise Consensus Criteria (Lake Louise Scoring System, LLSS) developed, revised in 2018; diagnosis of AMS requires patient to have recent gain in altitude plus headache and generally 1 other symptom, nausea or vomiting, fatigue or weakness, and dizziness or light-headedness; each symptom graded from 0 (none) to 3 (severe), score ≥3 considered positive for AMS; insomnia or sleep disturbance not a symptom of AMS because sleep issues occur frequently in healthy individuals who do not have AMS; sleep deprivation or insomnia at altitude is thought to be due to hypoxia; periodic breathing characteristic of initial sleep patterns at altitude with periods of apnea interchanged with periods of rapid cycle breathing; during apneic periods, oxygen saturation decreases, triggering both rapid breathing and periods of wakefulness; this nocturnal periodic breathing thought to be due to high peripheral ventilator drive and not linked to altitude illness; as contrasted with obstructive sleep apnea, these apneic periods centrally driven and are referred to as central sleep apnea if symptoms persist; acetazolamide and normal acclimatization improve sleep oxygen over time; currently believed that AMS exists on a continuum with high altitude cerebral edema (HACE); AMS mild self-limiting symptoms, other end of continuum is severe neurologic dysfunction associated with HACE; symptoms of AMS typically appear after 6-24 hours and peak after 1-2 days; generally self-limited due to most people's ability to adapt to the new hypoxic environment; progression of symptoms includes nausea and headache, not responding to antiemetics or analgesics, with increasing lassitude; major signs to watch for are ataxia and clouded consciousness, which if present, mandate immediate descent; unusual to develop symptoms if only at altitude for a few hours (eg, driving over mountain pass and stopping briefly at summit); important to observe for ataxia with AMS symptoms; precise pathogenesis not completely understood but seems to be result of hypoxia; AMS and HACE traditionally explained by "tight-fitting brain hypothesis" in which high altitude hypoxemia leads to vasodilation of cerebral blood vessels, which increases cerebral blood flow and volume, thought to cause impaired autoregulation, cerebral over-perfusion, increased capillary hydrostatic pressures, and vasogenic edema; at same time, hypoxemia triggers increased sympathetic activity leading to endothelial activation and increased capillary permeability, worsening vasogenic edema; rather than experiencing high altitude diuresis, patients with AMS tend to have activation of renin–angiotensin-aldosterone system and antidiuretic hormone (ADH) secretion, leading to expansion of extracellular fluid (ECF) volume, ultimately with increased cerebral edema; thought that there is inadequate buffering of volume by CSF; thus if patients have a "tight-fitting brain," meaning lower ratio of cranial CSF to brain volume, less ability for CSF to move into extra-cranial compartments, putting patient at risk for increased intracranial pressure and therefore AMS and HACE; recent evidence has challenged this theory; study published in 2009 using magnetic resonance imaging (MRI) did not find consistent difference in CSF volume, cerebral blood flow, or brain edema in patients with and without AMS when exposed to normobaric hypoxia; mild vasogenic edema may be the normal response to hypoxia with little bearing on the symptoms of AMS; edema also occurs in absence of a major breach of the blood-brain barrier; brain in AMS not characterized by any additional volume overload, thus making it unlikely that intracranial hypertension is a significant part of pathophysiology; new hypothesis for pathophysiology of AMS is that hypoxia triggers free oxygen radicals, which leads to failure of Na^+/K^+–ATPase pump, redistribution of vasogenic edema to intracellular space, astrocyte swelling, elaboration of nitric oxide, and perhaps activation of trigeminovascular system leading to AMS; HACE may represent progression of cytotoxic edema or major blood-brain barrier dysfunction and cerebral capillary stress failure; risk factors for AMS are history of AMS and individual susceptibility, rate of ascent, absolute altitude achieved, and low altitude residence before ascent; underlying cardiopulmonary diseases not shown to be risk factors, although limited evidence that obesity and lung disease may predispose to development of AMS; some studies show that heavy exertion on arrival may be associated with AMS; males and females equally susceptible, whereas older individuals tend to develop AMS less than younger adults; some people are more susceptible to developing AMS, while others are immune

Prevention: graded ascent; do not increase sleep elevation by more than 600 meters or 2000 feet per day above 10,000 feet; rest day every 2000 to 4000 feet; for tourists traveling to elevation to ski/hike/hunt, recommended to stop at lower elevation (eg, Denver if traveling to

Colorado) for the night prior to going to higher elevation resorts or mountain communities; estimated that this stop could reduce AMS by 35%-40%; normobaric hypoxia tents to sleep in for 14 days prior to travel advantageous based on certain studies; other measures of prevention include avoiding excessive alcohol and opiate intake and maintaining adequate hydration; dehydration at altitude common due to low humidity at altitude and decrease in plasma volume that occurs with ascent; overhydration should also be avoided, as there have been cases of severe hyponatremia reported due to excess water intake; several options for pharmacologic prophylaxis; acetazolamide current drug of choice; carbonic anhydrase inhibitor that facilitates acclimatization by stimulating respiration; interferes with CO_2 transport, creating an intracellular acidosis in cells of medullary chemoreceptors and enhances renal bicarbonate excretion, creating mild systemic metabolic acidosis; body then breathes deeper and faster to remove excess CO_2; standard dose 125-250 mg every 12 hours, generally taken 1 day before ascent and continued until descent is initiated, or for 2-3 days when maximum altitude has been attained; side effects include mild diuresis and paresthesia; because of its effect on CO_2 production, carbonated beverages (eg, beer, soda) will taste "flat" when taking acetazolamide; no such effect on wine or hard liquor; should be avoided in patients with major reactions to sulfa medications; another preventive medication in individuals who cannot take acetazolamide is dexamethasone; does not actually facilitate acclimatization, but rather helps to mask symptoms of AMS or HACE; more useful in improving symptoms while waiting for descent or evacuation; dose 2 mg every 6 hours or 4 mg every 12 hours; ibuprofen 1800 mg/day may also be effective at preventing AMS, but studies have yet to show superiority over acetazolamide or dexamethasone; general considerations for preventive medications include history of AMS, altitude profile, speed of ascent planned, difficulty of descent, and accessibility of medical care; general indications are rapid ascent from low altitude to >3000 meters or 10,000 feet in 1 day and history of AMS; treatment of AMS depends on severity; mild AMS may be treated by descent or avoiding further ascent, use of acetazolamide 250 mg every 12 hours, analgesics like acetaminophen and ibuprofen, and antiemetics; moderate AMS treated with descent and acetazolamide and/or dexamethasone 4 mg orally or intramuscularly every 6 hours; if descent not possible, patients should be treated supportively with supplemental oxygen if available and possibly a portable hyperbaric chamber; these recommendations are for AMS when in remote areas; when in a community with medical care available, patients can usually wait out symptoms over 1-2 days and take medication for symptoms such as headache or nausea; portable hyperbaric chamber for travel in remote locations made of synthetic material; use like a sleeping bag, use foot pump to pressurize chamber to 2 PSI (pounds per square inch), equivalent to reduction in altitude of about 5000 feet; unfortunately, foot pedal has to be pumped continuously to provide oxygen and flush out carbon dioxide, so short-term solution only

High altitude cerebral edema (HACE): least common but most deadly form of altitude illness; most commonly develops as a progression of AMS over 2-3 days, but has been known to occur within 24 hours; can occur very rarely in un-acclimatized individuals at 8000 feet; occurs most commonly with abrupt ascent to >12,000 feet; exact incidence of HACE unclear due to variations in definition and clinical diagnosis and wide range of rates of ascent; estimates range from 0.5%-1% of individuals with altitude illness; clinically, HACE characterized by evidence of global cerebral dysfunction; most commonly presents with ataxia and altered mental status; often preceded by severe AMS and also by evidence of high altitude pulmonary edema (HAPE), which can worsen the hypoxic insult; tandem gait test useful for diagnosing HACE at altitude; unlike AMS, severely increased intracranial pressure develops in HACE and death results from brain herniation; MRI studies in HACE typically show increased signal in white matter indicating vasogenic edema, particularly in splenium of corpus callosum; mechanism of prevention of HACE similar to AMS; treatment requires immediate descent or evacuation, high-flow oxygen, and dexamethasone; if descent not possible, portable hyperbaric chamber can be utilized if available to provide an equivalent descent of approximately 5000 feet; earlier the signs of HACE recognized, better the outcome; long-term sequelae have been reported in patients after recovery even after several years; early treatment generally results in good outcomes, but if coma occurs, mortality approaches 60%

High altitude pulmonary edema (HAPE): usually starts with increasing dyspnea and cough, progresses to orthopnea and pink frothy sputum production with worsening shortness of breath and cough; symptoms occur within 1-3 days of arrival at new altitude, usually >8000 feet; rarely occurs <8000 feet or if at altitude for >4 days, so other causes of symptoms should be explored (eg, pneumonia, pulmonary embolism) in those cases; in about 25% of cases, preceded by symptoms of AMS; 2 populations affected by HAPE, 1) well-acclimated mountain residents returning from lower elevations, called reentry HAPE, reported more in pediatric population, 2) rapid ascent of un-acclimatized "lowlanders;" recurrence of HAPE in individuals who have had 1 episode in the past about 60% upon return to elevation; similar to AMS, rate of ascent and individual susceptibility are major risk factors for HAPE development; prevalence reported as high as 7% with single-day ascents of 12,000-13,000 feet and higher with higher ascents; similar prevalence in Summit County in Colorado which has elevations of 9000-10,000 feet; chest X-rays classically show fine reticular infiltrates that are patchy and at times confluent, with right side showing infiltrates more often than the left in milder disease; no evidence of cardiomegaly or Kerley B lines, not a cardiac issue, not left ventricular dysfunction problem; right heart cardiac catheterizations done at altitude showed marked increases in pulmonary artery pressures, which precedes the edema, with normal wedge pressures and normal right atrial pressures; bronchoalveolar lavage shows protein-rich exudate and mild alveolar hemorrhages, whereas echocardiographic and catheterization studies show marked pulmonary hypertension

Mechanism: in susceptible individuals, hypoxia thought to trigger excessive pulmonary vasoconstriction; although not completely understood, theorized that uneven

vasoconstriction leads to focal or regional overperfusion, increased capillary pressure, and capillary leakage; also decreased clearance of sodium and water from alveolar space in HAPE; HAPE leads to worsened hypoxemia, setting off vicious cycle; to prevent, graded ascent is key; pharmacologic options usually reserved for HAPE-susceptible individuals; consider nifedipine extended release, inhibits hypoxic pulmonary vasoconstriction; typically started 1 day prior to ascent and continued for 2 days at maximum altitude, 20-30 mg every 12 hours; sildenafil 50 mg every 8 hours improves exercise performance at altitude, but only tadalafil 10 mg orally every 12 hours shown to prevent HAPE; consider administering any prophylactic agents for 1-2 days at sea level as test dose prior to travel so patients will know whether they tolerate the medication; treatment based on proximity to medical facility; most patients with HAPE in communities that have medical facilities can be treated simply with rest and oxygen and remain at their given altitude with close observation as long as their oxygen saturation is not significantly low; patients with 80% oxygen saturation or higher can be managed safely at altitude; these patients usually recover over 2-3 days; generally recommended that loop diuretics be avoided as most people are already intravascularly volume depleted; if in remote location, descent is recommended along with treatment with nifedipine; phosphodiesterase inhibitors have been shown anecdotally to also be effective, although no randomized studies to confirm efficacy; hyperbaric chambers if available are also effective; once HAPE has been treated and patient symptom-free and off medications, resumption of activities can be permitted as long as prophylactic medications are given and close observation maintained

Safety in air travel for patients with pulmonary disease: modern commercial airplanes not pressurized to replicate sea level pressures; regulations require aircraft to be pressurized to about 8000 feet or 2438 meters; they can go to >10,000 feet for short periods for safety reasons; 8000 feet chosen based on oxygen-hemoglobin dissociation curve data which demonstrates that oxygen saturation remains >90% despite drop in arterial oxygen tension in healthy people up to 8000 feet; in a patient who is already hypoxemic, this drop in barometric pressure and subsequent arterial oxygen tension may be enough to create significant oxygen deficits and respiratory fatigue; medical emergencies do occur in aircraft; 1 study indicated that these emergencies occur in about 1 out of every 604 flights or in 1 out of every 30,000 passengers; respiratory illnesses occur in approximately 12% of these emergencies and are most commonly associated with underlying comorbid conditions; respiratory issues are third most common reason for in-flight diversions due to medical issues; flight diversions costly and inconvenient for all travelers, so ensuring medical safety for patients with pulmonary issues by doing pre-flight screenings may be warranted

Physiologic changes during flight: 3 types; patient can become hypoxemic, hypercapnic, or develop increased pulmonary vascular resistance, resulting in worsening right ventricular failure; each of these can result in symptoms such as shortness of breath and air hunger; patients can also complain of chest pain, lightheadedness, palpitations, or paresthesia; even walking in flight for patients with pulmonary diseases may exacerbate these symptoms; other issues such as sleeping on flights, alcohol, or sedative intake may also exacerbate desaturations; study done in 2018 by Urgen[?] et al in *European Respiratory Review* recommends screening individuals who have high risk factors such as dyspnea on exertion, FEV_1 (ie, maximum amount of air able to be forcefully expired in 1 second) of <30% predicted, pre-existing requirement of ventilatory support, bullous lung disease, and comorbid conditions that may worsen hypoxemia (eg, cardiac disease); several tests to use for screening, including oxygen saturation, arterial blood gases, pulmonary function tests, walk tests, and hypoxic challenge testing; none of these are absolutely reliable; most patients can tolerate a few hours of hypoxemia without additional symptoms; in general, patients who have no oxygen requirement at sea level but have underlying respiratory disease very unlikely to need oxygen during flight, assuming no other concurrent illnesses; patients who require 2-3 L/min of oxygen supplementation at sea level should maintain this level during flight or increase it by 1 L/min if they become short of breath during flight, but they are generally safe to fly; patients who require ≥4 L/min at sea level are advised to have 1 of the previously mentioned pre-flight screening tests; if they require further supplementation during testing, then flying unadvisable; patients should also call the airline to discuss their oxygen need to ensure that the airlines can accommodate patients bringing compressed gas cylinder or portable oxygen concentrator on board

Suggested Reading

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Acute Kidney Injury

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Prevalence and impact: acute kidney injury (AKI) common; affects >5% of hospitalized patients and ≤30% of patients in ICU; patients with AKI have higher mortality; substantial cost of patient care, especially if AKI severe enough to require dialytic support

Terminology: acute renal failure (ARF) less commonly used term now; trying to communicate disease severity to patients and families difficult using ARF terminology; for example, seemed somewhat extreme to say patient with creatinine rise from 1.0 mg/dL to 1.3 mg/dL had ARF; people researching AKI and its natural history found it difficult to review notes, diagnostic classifications, and billing codes when term ARF used both for patients with mild creatinine increase and those requiring dialytic support; patients who have lost kidney function over course of hrs to days have AKI; definition now based on either increase in creatinine (drop in glomerular filtration rate [GFR]) or decrease in urine output; increase in creatinine by as little as 0.3 mg/dL within few days, increase in creatinine by 50% from baseline value, or decrease in urine output to <0.5 mL/kg/hr for several hrs enough to diagnose AKI; *eg*, 70-kg patient who makes <35 mL/hr for shift would be considered to have stage 1 AKI; rise in creatinine by >50% or >2 mg/dL to 3 mg/dL, urine output decrease for longer period of time, or anuria enough to characterize patient as having higher stages of AKI (stage 3 worst); even small changes in creatinine (*eg*, rise of 0.3 mg/dL) significant because they increase mortality

- Oliguria: <500 mL of urine over course of day; worse prognosis than for nonoliguric patients
- Anuria: <50 mL of urine over course of day; worse prognosis

Diagnosis: important to know baseline creatinine value; if patient has elevated but stable baseline creatinine, may be decreased renal reserve and patient at risk of superimposed AKI, but may be no active, acute process; oliguria and anuria never considered stable, considered worsening because unsustainable and will lead to volume overload

Creatinine clearance and GFR: clearance=volume of blood cleared of substance over some period of time; normal creatinine clearance 90 mL/min (90 mL of blood cleared of creatinine each min); creatinine filtered at high rate at glomerulus, and in normal renal function, only small portion secreted into tubules; creatinine clearance considered important proxy for GFR; creatinine molecule itself produced in muscle tissue, and in steady state, level (concentration) of creatinine in serum function of patient's total muscle mass; *muscle mass* — epidemiologically related to age, sex, and race; older Caucasian woman with low muscle mass and creatinine of 1.2 mg/dL likely has very low creatinine clearance compared with young African American man with large muscle mass and same creatinine; most laboratories in processing samples have access to patient age and sex information but not necessarily race, so reported laboratory values often include calculated or estimated GFR (eGFR) for African Americans as well as eGFR for non-African Americans; calculation of eGFR considered valid when creatinine in steady state, not when actively changing from day to day; some medications (*eg*, trimethoprim, cimetidine) may interfere with secretion of creatinine into tubules but have no effect on GFR; administration of trimethoprim may increase serum creatinine level by 0.5 mg/dL, but this change does not necessitate extensive evaluation for AKI; creatinine clearance imperfect test because affected by factors such as alterations in muscle mass

Blood urea nitrogen (BUN): urea subject to even more imperfections than creatinine clearance as proxy for kidney function; patients with upper-gastrointestinal (GI) bleeds, high-protein diet, or those taking catabolic steroids often have elevated BUN despite unchanged or decreased kidney function

Presentation and evaluation: first sign of AKI often lab abnormality detected on routine blood tests or at time of admission; patients may or may not have localized symptoms (*eg*, changes to urine, or systemic systems such as rash)

- Signs and symptoms: *AEIOU mnemonic for AKI signs* — **a**cidosis, **e**lectrolyte abnormality, **i**ntoxication or **i**ngestion, **o**verload of volume, and **u**remia; signs and symptoms of abnormal kidney function may manifest as cardiac issues (*eg*, arrhythmia related to hyperkalemia, pericarditis detectable by pericardial rub on cardiac auscultation), neurologic symptoms related to uremia (*eg*, loss of appetite, nausea and vomiting, asterixis, altered consciousness, sluggishness, grogginess); worst-case scenario for uremia encephalopathy with seizures; less commonly, hematologic complications (bleeding due to uremic platelet dysfunction); perform thorough history and physical exam; focus on medication changes, oral intake, GI symptoms, and volume loss (*eg*, diarrheal illness, fevers), and other systemic symptoms; basic vital signs (*eg*, fever, blood pressure [BP], possibly orthostatics, heart rate); volume status (jugular venous pressure, evidence of pulmonary edema on chest auscultation, ascites, lower-extremity edema, overall volume status, changes in skin and joints suggestive of systemic illness)
- Laboratory studies: most useful laboratory studies include basic or comprehensive metabolic panel, complete blood

count with differential, urinalysis with microscopy (for evidence of casts); if patient oliguric, may be helpful to measure urine sodium, creatinine, and urea to calculate fractional excretion of sodium (FENa); for oliguric patients who have been taking diuretics, FENa may be falsely elevated, but fractional excretion of urea can be measured and may be helpful; imaging can be helpful, especially to rule out acute obstructive process; imaging of choice, ultrasound of retroperitoneum and bladder; imaging provides information without radiation and at relatively low cost; can provide information regarding echogenicity and other clues to chronicity of kidney disease; if thorough noninvasive evaluation of AKI unrevealing, biopsy may be considered

Etiology and differential diagnosis: classified anatomically as prerenal, intrinsic renal, or postrenal

Postrenal (obstruction of urinary tract): in elderly man, common issue may be enlarged prostate leading to bladder-outlet obstruction; in woman with abdominal or uterine tumor, bilateral ureteral obstruction may occur; anything that causes obstruction of urinary tract should be considered; kidney stone can cause hydronephrosis, presents with colicky flank pain; patient with hemorrhagic cystitis may have blood clots in bladder and resultant bladder outlet obstruction; radiation or some lymphoproliferative diseases can cause retroperitoneal fibrosis and ureteral obstruction; although renal ultrasound simplest study, bladder scans increasingly used in hospitals to evaluate postvoid residual to assess urinary retention; placement of bladder catheter can be both diagnostic (if urine output large in volume and brisk upon placement of catheter) and therapeutic (if bladder-outlet obstruction present)

Prerenal (functional azotemia): anything that causes low perfusion pressure to renal parenchyma; differential can be as broad as low-volume state after big workout without adequate fluid or solute intake or following diarrheal illness with inadequate replacement of fluid losses from GI tract; other causes of low blood perfusion to kidney include low cardiac output (systolic heart failure), distributive shock from sepsis or hemorrhage; patients with portal hypertension often have low systemic BP and physiology comparable to distributive shock, which ultimately leads to low perfusion of kidney; if patient oliguric and has not been administered diuretics, measurement of FENa will often be low (<1%); high FENa (>2%) suggests intrinsic kidney injury

Intrinsic: causes include acute tubular necrosis (ATN), acute interstitial nephritis (AIN), glomerulonephritis (GN), and many other possible considerations

ATN: many different mechanisms can cause injury to tubular cells, specifically proximal tubular cells; ischemic ATN most common, which results from low blood flow from prerenal state that has gone on for long time or extremely severe; because kidney has several autoregulatory mechanisms to maintain normal blood flow into glomerulus and to maintain normal or steady GFR, any factor that inhibits typical autoregulation puts patient at risk for ischemic ATN; common examples include administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs); particularly high risk in older patients and those with atherosclerotic vascular disease); other etiologies of ATN include sepsis or specific toxic exposure by such things as rhabdomyolysis or hemolysis, which would lead to myoglobin or hemoglobin, respectively, making their way into tubules and causing tubular necrosis and tubular injury; other common drugs (*eg*, aminoglycosides, gentamycin, tobramycin, antifungal amphotericin B); various chemotherapeutic drugs, especially those containing platinum; administration of high-osmolar contrast, especially in high volumes to patient with poor renal perfusion, can cause AKI and ATN because iodinated contrast can be tubular toxin; however, most modern contrast given in low volumes to patient whose volume status has been optimized for good renal perfusion may not be major risk; elevated creatinine and abnormal kidney function not absolute contraindications to use of contrast as long as risks and benefits considered

AIN: classic triad includes rash, peripheral eosinophilia, and fever; less than one-third of patients actually have this triad; patient who has been exposed to particular drug class and develops sterile pyuria with white blood cells (WBCs) and WBC casts in urine should be considered at risk for AIN; most common drugs that can predispose to AIN are beta-lactam antibiotics and fluoroquinolones; proton pump inhibitors and allopurinol also can cause AIN; several autoimmune diseases (*eg*, sarcoidosis) and some liquid tumors (*eg*, leukemia, lymphoma) can predispose to AIN; whether infectious (pyelonephritis) or in response to drug or autoimmune process, patients have WBC casts

GN: most glomerular diseases present over longer period, leading to subacute kidney injury or chronic kidney disease; in some cases, rapidly progressive glomerulonephritis (RPGN) can present acutely; urine studies show both blood and protein; patient has evidence of systemic process (*eg*, skin rash, joint pain, hemoptysis, other organ dysfunction); urine studies and urine microscopy to look for red blood cell (RBC) casts (hallmark of GN), immunologic serologies should be evaluated, including antineutrophil cytoplasmic antibody (ANCAs); most labs now measure specific antibodies called antiproteinase 3 (PR3) and antimyeloperoxidase (MPO) antibodies; antiglomerular basement membrane (anti-GBM) antibodies may be sent, along with complements, in evaluation of immune-mediated glomerular disease

Crystal nephropathy: results from substance that crystallizes within tubules and causes obstruction of urine flow within renal tubules, and ultimately kidney injury; commonly associated drugs include intravenous (IV) acyclovir, indinavir, high-dose vitamin C; reports of high oxalate loads from multiple liters of iced tea with oxalate can lead to calcium oxalate crystallization in tubules; patients with solid or liquid tumors and high tumor burden with subsequent tumor lysis from chemotherapy or under spontaneous circumstances may release large amount of uric acid, which may then crystallize, causing AKI; other findings in tumor lysis syndrome include, in addition to hyperuricemia, hyperkalemia and hyperphosphatemia; reports of phosphate-containing bowel preparations and enemas that have ultimately crystallized and led to kidney

injury; if any concern about renal insufficiency, phosphate enemas and bowel preparations should be avoided

Vascular injury

Renal artery stenosis or renal vein thrombosis: can lead to infarction of renal parenchyma; symptoms often include flank pain, gross hematuria, or microhematuria; elevated creatinine and lactate dehydrogenase (LDH)

Vasculitis (eg, polyarteritis nodosa): affects larger vessels than glomeruli and can be considered

Thrombotic microangiopathy: common etiologies include hemolytic uremic syndrome (HUS), most commonly after diarrheal illness with *E coli* or thrombotic thrombocytopenic purpura (TTP), which can result from medication exposures (*eg*, clopidogrel, calcineurin inhibitors [*eg*, cyclosporine or tacrolimus], or chemotherapeutic agents [*eg*, gemcitabine]); other mechanisms include preeclampsia and hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome; and malignant hypertension related to scleroderma or cocaine use; *triad of HUS* — anemia, thrombocytopenia, and renal insufficiency after diarrheal illness from *E coli*; *pentad of TTP* — microangiopathic hemolytic anemia, thrombocytopenia, renal insufficiency, fever, and neurologic symptoms; early recognition of TTP important because plasmapheresis may improve outcomes

Cholesterol emboli after procedure in aorta or coronary arteries: syndrome of cholesterol or atheroembolic disease may present days or wks later; characterized by hematuria, hypocomplementemia, clinical stigmata of embolic disease (livedo reticularis or splinter hemorrhages)

Other etiologies of AKI that disrupt renal function via multiple mechanisms:

NSAIDs: commonly used and with good effect; can cause prerenal kidney injury, ATN, AIN, and some glomerular diseases

Dysproteinemic disease (*eg*, multiple myeloma): can cause several different kidney problems, such as glomerular disease, proteinuric nephrotic syndrome, or tubular obstruction with myeloma kidney

Cardiorenal syndrome: can result from poor systolic function and low perfusion pressure presenting as prerenal azotemia, but diastolic dysfunction or right ventricular dysfunction may lead to poor outflow from renal parenchyma and renal venous hypertension; treatment involves inotropic support and, in some cases, diuretic management to optimize cardiac output and normal systolic and diastolic function

Hepatorenal syndrome: can result from any process that causes portal hypertension; often from cirrhosis and hepatic fibrosis; *typical physiologic response to portal hypertension* — splanchnic vasodilation, peripheral vasodilation, low BP, and low perfusion pressure into kidney; depending on severity and duration, management typically involves efforts to increase renal perfusion with midodrine, octreotide, or colloid infusion

Abdominal compartment syndrome: seen in patient with tense ascites or large intraabdominal mass; multiple visceral organs compressed, including inferior vena cava, renal vein, renal parenchyma, and perhaps renal artery; results in poor blood flow through renal parenchyma, low urine output, and worsening kidney function

Management of AKI: first step, optimizing renal perfusion pressure and blood flow through kidney; hypovolemic patient may be given volume; patient with systolic heart failure may be given inotrope; discontinue obvious toxic exposures (*eg*, NSAIDs, aminoglycosides) if possible; review medication list to confirm proper dosing; many antibiotics cleared by kidney and require dose adjustment in patients with decreased kidney function; patients with complications of renal insufficiency or AKI may require dialytic support; remember AEIOU mnemonic (A=severe acidosis, E=electrolyte abnormality [most commonly hyperkalemia], I=ingestion or intoxication [some substance that can be cleared by dialysis], O=overload of volume [especially in oliguria or anuria and progression towards pulmonary edema and respiratory failure], U=uremia with complications); depending on patient's hemodynamics and availability of various modalities, intermittent hemodialysis or continuous renal replacement therapy may be offered; peritoneal dialysis not typically used in AKI

Prognosis for AKI: depends on underlying kidney function and preexisting chronic kidney disease, comorbidities, and natural history of other processes that led to AKI; some patients recover renal function and return to normal baseline creatinine; others recover some function but have creatinine above prior baseline as result of some degree of chronic kidney disease going forward

Appropriate timing for renal consultation: when patient has systemic illness and glomerular disease considered, rapid evaluation with serologic testing and possibly biopsy could guide management with immunosuppressive therapy to change outcomes (pulmonary renal syndrome and ANCA vasculitides); patients with declining urine output at risk for developing volume overload and hypoxemic respiratory failure from pulmonary edema; early involvement of nephrologist to consider dialytic therapy for volume management; clinical instability (*eg*, with hyperkalemia, especially with poor urine output) could lead to cardiac arrhythmia and clinical instability that would warrant early dialytic support

Future directions: several biomarkers have been studied, some commercially available; key to recognize and understand how new biomarkers can be used to recognize AKI, perhaps at earlier stage so earlier intervention can occur; keep in mind importance of avoiding excessive testing and unnecessary costs

Suggested Reading

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Chronic Kidney Disease and Tubulointerstitial Diseases

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Chronic kidney disease (CKD): presence of kidney damage marker and/or reduced estimated glomerular filtration rate (eGFR) present for >3 months; *markers of kidney damage* — proteinuria; albuminuria; abnormal urine sediment — *eg*, hematuria; electrolyte or other abnormalities caused by tubular dysfunction; histologic abnormality of kidney (typically found on renal biopsy); structural abnormality (typically found on screening exam, *eg*, CT scan or ultrasound)

eGFR — determined by measuring serum creatinine value of blood sample; value used as part of regression formula to convert serum creatinine into eGFR; in CKD, reduced eGFR <60 mL/min, normalized for body surface area of 1.73 m^2

Kidney Disease Improving Global Outcomes (KDIGO) guidelines: allow staging of CKD and consider 2 major features: eGFR (stages people from 1 through 5) and within those subcategories of eGFR, further classifies patients by presence and degree of albuminuria; system provides prognostic information; patients at higher G stages and those with higher degrees of albuminuria at risk for progression of CKD as well as for other morbidities and mortality, especially cardiovascular disease (CVD)

eGFR stratification: G1 — normal or high GFR (>90 mL/min); G2 — mildly decreased GFR (60-90 mL/min); G3a — mild to moderately decreased GFR (45- 59 mL/min); G3b — moderately to more severely decreased GFR (30-44 mL/min); G4 — more severely decreased GFR (15-29 mL/min); G5, or kidney failure (eGFR <15 mL/min)

Persistent albuminuria categories: used on top of eGFR categories; A1 — normal or mildly increased albumin level in urine (<30 mg/g creatinine on spot urine albumin-to-creatinine ratio); A2 — moderately increased urine protein or urine albumin (30-300 mg/g creatinine); A3 — severely increased albuminuria (>300 mg/g creatinine)

Epidemiology and demographics: about 7% of US adults aged >20 yr have some degree of CKD, especially eGFR <60; if include albuminuria, incidence increases to 12%, showing CKD quite prevalent; *risk factors associated with CKD* — diabetes mellitus, hypertension (HTN), obesity, CVD, and infections (*eg*, HIV or hepatitis C); about 35% of Americans aged >60 yr have some degree of CKD; patients at stage 5 and end-stage renal disease (ESRD), facing need for dialysis or transplantation, most common causes in US — diabetic nephropathy (40%-50%), HTN (20%-30%), and glomerulonephritis (5%-6%); although incidence of patients entering US dialysis population has seemingly plateaued in recent years, mortality of this patient population has improved, so prevalence of patients on dialysis in US continues to increase

Screening: controversial subject with differing recommendations from professional societies; because CKD asymptomatic until quite severe, only way to detect CKD is through screening — likely includes testing for urine albumin, measuring serum creatinine, perhaps renal ultrasound

American College of Physicians (ACP): recommends against screening for CKD in asymptomatic adults, certainly in those without CKD risk factors; ACP has also questioned value of screening patients with known risk factors; argument is that screening programs or early detection of CKD has not been shown to have outcome benefit

American Society of Nephrology: emphasizes importance of screening for CKD in all adults; screening — serum creatinine and urine test to look for urinary abnormalities, perhaps supplemented by renal ultrasound

Referral to nephrologist: when diagnosis uncertain about etiology of patient's CKD, nephrologist may be valuable; may need to perform renal biopsy to exclude treatable cause (*eg*, glomerulonephritis) or underlying genetic disease that requires specific treatment and detection; patients with more advanced CKD (stage 3b or above) need counseling about prognosis and risk stratification for CKD progression; in shared-decision model (with patient's family), data show better outcomes with early referral to nephrologist and early preparation for renal replacement therapy

Complications of CKD:

CVD: most common cause of death for patients with CKD; CKD and albuminuria among greatest risk factors for excess cardiovascular (CV) morbidity and mortality; aggressive management of cardiac risk factors may show significant benefits in patients with CKD at highest risk for morbidity and mortality

HTN management: evolving topic; Eighth Joint National Committee (JNC 8) recommended blood pressure (BP) target <140/90 for patients with CKD without proteinuria; for patients with proteinuria, some experts recommended BP goal of <130/80 — better results and lower risk of CKD progression when treated to lower BP targets, especially with angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers

(ARBs); SPRINT trial raised doubts about whether these goals may be too high for patients; BP goals for patients with CKD need to be managed aggressively; consider ACEis or ARBs for first-line therapy, especially in patients with proteinuria

- Lipid abnormalities: elevated triglyceride levels and lower HDL levels with variable LDL levels — depend upon numerous factors; dyslipidemia associated with higher risk of CKD progression, but no intervention trials have shown that treatment of dyslipidemia slows CKD progression; studies have demonstrated that treatment with statins in patients with GFR <60 and albuminuria reduces adverse CV outcomes to similar degree as in patients with normal kidney function; KDIGO group recommends treatment with statins for patients aged >50 yr with GFR <60 and/or albuminuria; data less clear in patients with ESRD; major studies that have looked at treating hemodialysis patients with statins have failed to demonstrate benefit in improving CV morbidity and mortality, despite control of LDL levels; no current recommendation to treat existing patients on dialysis with statins
- CKD mineral and bone disorder spectrum: kidney is major homeostatic organ for maintaining calcium (Ca) and phosphorus (P) balance; normal homeostatic mechanism disrupted as kidney function declines — results in significant alterations in bone mineral metabolism and leads to vascular calcification; encompasses changes in patients with CKD from disruptions in Ca and P metabolism
  - Pathophysiology — Ca and P homeostasis regulated by 3 hormones: parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and active 1,25-dihydroxyvitamin D; as GFR begins to decline, elevation in FGF23 levels starts to occur; FGF23 increases renal P excretion — as GFR falls, helps maintain normal P homeostasis and levels; over time, increased FGF23 levels and decreased nephron mass lead to impairment of active 1,25-dihydroxyvitamin D production from precursor hormone (25-hydroxyvitamin D); decrease in 1,25-dihydroxyvitamin D results in lower-intestinal absorption in Ca and P; combination of decreased renal P excretion and elevation of Ca–P product that can lead to precipitation of Ca-P results in reduced serum Ca level; higher P level and lower Ca level stimulate PTH secretion; PTH reduces Ca excretion and augments renal P clearance; early on, PTH elevation can maintain serum Ca levels within normal limits; occurs at expense of increasing bone turnover; as CKD progresses, kidney becomes unable to compensate for increased release of P from bone, P levels begin to increase, and high levels of P stimulate PTH production, further stimulating bone breakdown
  - Laboratory abnormalities: Ca, P, PTH, and 25-hydroxyvitamin D levels; as GFR drops (usually stage 3b to 4), elevations in P and slight decreases in Ca are seen; progressive declines in 1,25-dihydroxyvitamin D levels and elevations of PTH occur; lower Ca, higher P, elevated PTH levels, and low 1,25-dihydroxyvitamin D levels characteristic laboratory abnormalities in abnormal kidney function (stage 3b to 5 CKD)
  - Vascular calcification: calcification occurs in all vascular trees, including coronary arteries; calcification burden worsens as CKD progresses; *downstream effects* — reduced vascular compliance; contributes to increased prevalence of left ventricular hypertrophy; microvascular changes that can result in ischemia of organs and other tissues; avoidance of vascular calcification via maintenance of normal Ca, P, and PTH levels throughout spectrum of CKD critical for improving outcomes
  - Renal osteodystrophy: alteration of bone morphology in patients with CKD; high bone turnover (osteitis fibrosa cystica) — patients may have bone cysts, bone pain, and increased risk of fractures that heal poorly; low bone turnover (adynamic bone disease) — patients typically have suppressed PTH levels and susceptibility to poorly healing fractures; patients with CKD mineral and bone disorders may also have osteomalacia or osteoporosis
  - Management: primary goal — maintenance of Ca, P, PTH, and vitamin D within normal ranges; first step — monitoring these levels at regular intervals; patients with CKD stage 3b or beyond have these parameters measured at least quarterly; KDIGO guidelines focus on attempts to normalize PTH levels; first step — correct 25-hydroxyvitamin D deficiency — hopefully will allow some normalization of serum Ca and P to lessen stimulus for PTH secretion; first step — use of nutritional vitamin D analog (*eg*, ergocalciferol) to supplement 25-hydroxyvitamin D levels; if PTH levels still elevated after normal range of 25-hydroxyvitamin D obtained, active vitamin D (*eg*, calcitriol or calcitriol analog) added to further suppress PTH levels; use of active 1,25-dihydroxyvitamin D risks development of both hypercalcemia and hyperphosphatemia from increased absorption of Ca and P; monitor for hypercalcemia and hyperphosphatemia when using active vitamin D analogs; also important to limit dietary P intake; use of active vitamin D analogs may increase intestinal P absorption — can lead to hyperphosphatemia; dietary P can be found in many processed foods — should be avoided; dietary counselor should be consulted to help guide patients; in some cases, especially as CKD advances to stages 4 and 5, serum P may become elevated, requiring dietary P binder; dietary P binders taken with meals and binder combines with dietary P to form insoluble, easily excretable compound; several different P binders; Ca-containing binders, especially when used with vitamin D, can lead to hypercalcemia; many experts advocate for not using Ca-containing dietary P binders; other classes of dietary P binders include sevelamer (polymer) and many newer compounds based on iron moiety (*eg*, ferric citrate), which may also have added benefit of supplementing iron levels
- Anemia: kidney prime secretor of erythropoietin (hormone responsible for stimulating bone marrow to make red blood cells [RBCs]); ability to produce erythropoietin diminishes as kidney disease progresses; changes in bone marrow sensitivity to erythropoietin and decreased RBC lifespan contribute to anemia; first step in diagnosis and management — determine if other causes of anemia; screen for blood-loss anemia

and vitamin (*eg*, B12, folate) and iron deficiency; in absence of these, likely anemia associated with CKD — typically normocytic; patients usually become symptomatic only after eGFR falls below 30

Management: look at iron stores; KDIGO recommends transferrin saturations >30% and serum ferritin levels >500 ng/mL in patients with CKD whose anemia not due to other causes; higher iron levels required in patients with CKD allow efficient response to erythropoietin; first step in management of anemia of CKD — iron supplementation with oral or intravenous (IV) iron; numerous IV irons available — all effective in increasing iron levels; if patient remains anemic after iron supplementation, erythropoietin-stimulating agents (ESAs) can be effective in improving anemia and associated symptoms; recently, concerns associated with risks and expenses of ESAs; *black box warning for patients* — risk of increased mortality and/or tumor progression in patients with active malignancy, and higher risk of thromboembolic and serious CV events, especially when administered to patients with hemoglobin levels >11 or history of stroke; need to maintain careful monitoring of hemoglobin in patients treated with ESAs; target hemoglobin levels between 10 g/dL and 12 g/dL

Metabolic acidosis: common; occurs in later stages of CKD; results from diminished ability of kidney to regenerate new bicarbonate; strong association between lower serum bicarbonate level and adverse clinical outcomes, including CKD progression and mortality; small prospective trials have demonstrated slower progression of CKD and better outcomes in patients treated with some form of alkali (usually sodium bicarbonate or sodium citrate) to increase serum bicarbonate to ≥23 mEq/L; KDIGO guidelines recommend to use alkali therapy to supplement serum bicarbonate to normal level; important to recognize these are sodium salts; additional sodium load can contribute to volume overload — should be watched for and treated as necessary

Acute kidney injury: patients with CKD are at high risk; often caused by nephrotoxins; nephrotoxins that need to be carefully monitored for and avoided — *eg*, drugs such as NSAIDs, some chemotherapeutic agents, antibiotics, and iodinated contrast material; clinicians should be vigilant in prescribing medications to patients with CKD; nephrologist should be consulted to make sure drug safe and dosed appropriately for patients with CKD; acute kidney injury can be detrimental to patients — may not recover kidney function, hastening progression to ESRD; even if they recover from acute kidney injury, rate of progression of CKD increased; maintain high vigilance for exposure to nephrotoxic insults

ESRD: associated with high mortality rate — about 10 times higher than for any age-matched control; drivers for mortality include CVD and infection; given high rate of mortality and morbidity associated with dialysis, patients need to be closely monitored and counseled as they approach planning stage for ESRD; better planning and counseling may yield better outcomes; planning for ESRD treatment should begin about 1 yr before anticipated start of dialysis; planning period provides appropriate counseling and education — patients can make shared, informed decision, and ensures appropriate screening for comorbidities and preparation for dialysis or transplant; in most practices, patients with eGFR <30 mL/min begin to receive education regarding treatment options; incidence of kidney disease and dialysis initiation increasing most rapidly among patients who aged >75 yr; this group has high burden of comorbid conditions and poor functional status; considerations in decisions about initiation of renal replacement therapies this population — comorbid medical conditions, expected outcome of starting renal replacement therapy, current functional status and expected status after starting dialysis, and patient and family preferences regarding goals of care; extremely important; these discussions take time and evolve over time

Hemodialysis: for most patients in the US, hemodialysis done at center; patients has dialysis sessions 3 times weekly, each lasting 3.5 to 4 hours; 2 major functions of hemodialysis — 1. remove solutes and uremic toxins, and to maintain electrolyte and acid-based homeostasis, and 2. remove excess fluid through ultrafiltration; patients also receive dietary counseling, social work visits, case management, and other care at dialysis center

Dialysis access: patients who opt for hemodialysis need to have dialysis access in place; 3 forms of dialysis access — 1. arteriovenous (AV) fistula, native access created by anastomosis between patient's artery and vein (typically in upper or lower arm); 2. AV graft — artificial graft material connects artery and vein in arm; 3. indwelling hemodialysis catheter; ideally, patients should get AV fistula and be referred for this at the earliest stage after choosing hemodialysis; AV fistulas require maturation and time to heal before ready for use (8 weeks or longer before fistula is usable for dialysis); patients have better outcomes on hemodialysis when dialyzed with AV fistula — lower rate of complications (especially infections) compared with AV grafts or indwelling catheters

Home hemodialysis: advances in technology allow for dialysis machines in home; patients can have more frequent sessions and at night when asleep; specific criteria for allowing patients to go home with hemodialysis — must be evaluated by nephrologist during counseling when dialysis options discussed

Peritoneal dialysis: dialysate solution instilled into abdominal peritoneal cavity through indwelling catheter; peritoneal membrane allows for solute and fluid transfer through osmosis and diffusion to enable dialysis; effective — clinical outcomes, including morbidity and mortality, very much equivalent for patients undergoing peritoneal dialysis and hemodialysis; diabetic patients, especially those with poor glucose control, may do slightly better on hemodialysis; risk for peritonitis (infection from peritoneal dialysate solution) greatest concern; uncommon — occurs once to twice every 2 to 3 yr; peritonitis usually effectively treated with intraperitoneal antibiotics — can be infused during peritoneal dialysis treatment

Advantage of both peritoneal and home hemodialysis: patients have greater autonomy and freedom from having to go to dialysis center 3 times a week for extended time; however, home-based modalities also

require greater patient effort in terms of self-care and also rely on caregivers and family members for help

Nondialytic therapy (conservative management): some patients with ESRD may opt not to pursue dialysis or transplant; includes management of symptoms and complications of ESRD; anemia management, good control of electrolytes, and good nutritional support, but patients will not undergo dialysis; some elderly patients with high comorbid disease burden may live as long on conservative management as on dialysis; some data indicate that any increase in longevity by using dialysis in sicker patients may be outweighed by the increased time spent in hospital or dialysis center; nondialytic therapy usually done as part of multidisciplinary team including palliative care and hospice expert; can be good option for patients with significant disease burden

Transplantation: patients with ESRD who receive kidney transplants have markedly better outcomes — improved life expectancy and quality of life; transplantation preferred therapy for renal replacement therapy in eligible candidates; unfortunately, not enough organs for all patients with ESRD; many patients who require deceased donor transplant may have prolonged waiting times of 7 yr or longer; best option is preemptive transplant — when living donor can be identified before patient requires dialysis or transplant, avoiding need for dialysis; important to give transplant centers enough time to adequately assess eligibility and safety of transplant; patients typically referred when eGFR <20; transplant process begins with careful pretransplant evaluation, ensuring candidates suitable for procedure; evaluation includes screening for infectious disease, cancers, and CVD, and ensuring adequate social support; after transplant, transplant nephrologist will manage patient for 3 to 6 weeks before transferring care back to primary care doctor or local nephrologist; transplant centers continue to monitor patients closely to ensure immunosuppressive medications re dosed appropriately and that patients screened for other conditions associated with risks post transplant, *eg*, skin cancers, other malignancies, infections, and CVD

Key points for CKD:

1. CKD is a prevalent condition caused by comorbidities such as diabetes, hypertension, and obesity. Patients with CKD should be staged and, at some point, referred to a nephrologist for expert care when their GFR reaches stage 3b or worse or when the diagnosis is uncertain.
2. CVD is the primary driver of mortality in patients with CKD, and aggressive risk-factor modification including good control of lipids and BP, as well as screening for coronary disease, should be mandatory in these patients to try to improve outcomes.
3. Other common complications of CKD include bone-mineral metabolism disorders, anemia, and metabolic acidosis. These typically occur when the GFR is ≤30 and can most effectively be managed by a nephrologist in concert with the primary care doctor.
4. Many options exist for renal replacement therapy. Patients should be counseled extensively about these options, and a shared-decision model should be used so patients can make the best-informed choice for their own health and well-being.

Tubulointerstitial diseases: primarily affect renal tubules and interstitial material surrounding them; can be acute (acute interstitial nephritis) or chronic, leading to chronic tubulointerstitial disease that may progress to ESRD; most commonly encountered chronic tubulointerstitial diseases have progressed from acute interstitial nephritis or other acute insult; chronic urinary tract obstruction can also lead to chronic tubulointerstitial changes that manifest themselves as CKD

Clinical manifestations: as with all renal diseases, symptoms and physical findings may be minimal or absent, unless associated with an underlying active disease, such as collagen vascular disease (*eg*, sarcoidosis, Sjögren syndrome, systemic lupus erythematosus [SLE]); diagnosis often triggered by laboratory abnormalities, *eg*, decline in GFR may be from obstruction, microvascular damage, fibrosis, or progressive disease of tubules

Specific interstitial disease may preferentially cause injury to proximal tubule; proximal tubular damage leads to tubular abnormalities including incomplete absorption and wasting of glucose in urine and abnormalities in handling of phosphate, uric acid, bicarbonate, and amino acids in urine; leads to wasting of these substances in urine and hypophosphatemia; glucose seen in urine despite serum glucose level within normal limits; if occurring in proximal tubule, may lead to Fanconi syndrome; other manifestations of chronic and acute tubulointerstitial diseases may include normal anion gap, metabolic acidosis, or renal tubular acidosis that may involve the proximal or distal tubules, and decreased ammonia production

Inability to concentrate urine — characteristic of tubulointerstitial disease; often, early in disease, patients complain of nocturia and increased thirst and urination; urinalysis may show low degrees of proteinuria — typically, tubular proteins with molecular weights generally lower than albumin, and proteinuria values usually <2 g/day

Other manifestations may include hypo- or hyperkalemia, depending on tubular defect, and anemia due to injury of tubules and decreased erythropoietin production; all can be clinical clues to presence of tubulointerstitial disease; consider diagnosis of tubulointerstitial disease in patients with unexplained chronic or acute kidney injury, especially those with more bland urinalyses without cellular elements, or perhaps showing some white blood cells (WBCs) or WBC casts; renal ultrasound may be normal or may show small, more atrophic kidneys associated with chronic condition; in some cases, kidney biopsy and referral to nephrologist necessary for definitive diagnosis

Autoimmune causes: sarcoidosis, Sjögren syndrome, systemic SLE, IgG4-related disease, and tubulointerstitial nephritis with uveitis (TINU); Sjögren syndrome, sarcoidosis, and SLE most common

Sjögren syndrome — can cause lymphocytic and plasmacytic infiltration in kidneys; diagnosis often confirmed by biopsy showing granulomas

Sarcoidosis — can lead to more advanced, severe disease; important to understand that kidney damage can occur through other mechanisms, *eg*, retroperitoneal fibrosis, hypercalcemia, hypercalciuria, and nephrolithiasis; biopsy shows characteristic granulomas; usually occurs in context of other systemic disease

SLE — often concomitant with associated glomerular disease or other manifestations of SLE and typically found on kidney biopsy

IgG4-related disease — larger group of diseases with characteristic features; infiltration of many organs by lymphoplasmacytic infiltrate of IgG4-positive plasma cells; these cells lead to resultant end-organ fibrosis and, often, elevated serum IgG4 levels; occasionally, may also be associated glomerulonephritis

Toxic causes: typically seen with heavy metal exposure (*eg*, mercury, lead, cadmium); rarer disease forms that occur in certain areas, including Balkan endemic nephropathy, Mesoamerican nephropathy (central America), and form occurring in India; these diseases not well characterized, but lead to chronic tubulointerstitial phenotype

Hereditary causes: many hereditary diseases — medullary cystic kidney disease, mitochondrial disorders, and nephronophthisis; rare; usually diagnosed in early adulthood or even infancy

Infection-related causes: quite varied — can include polyoma BK virus, usually in patients who have had kidney transplant; others more commonly seen in adults include cytomegalovirus, Epstein-Barr viruses, fungal infections, *Legionella* infections, tuberculosis, and toxoplasmosis; any form of pyelonephritis can lead to both acute and chronic interstitial nephritis

Malignancy-related causes: usually associated with hematologic malignancies (*eg*, leukemias and lymphomas) — cancer cells invade the kidney, leading to large kidneys (detectable on ultrasound), along with acute and chronic renal failure

Medication-induced causes: probably most common; many drugs lead to both acute and chronic tubulointerstitial diseases; acute interstitial nephritis often caused by drugs such as antibiotics that can be associated with acute decrease in GFR, perhaps some WBCs or WBC casts in the urine; concomitant use of these drugs and timing, as well as development of acute kidney injury, can be key in determining whether acute interstitial nephritis due to medication exposure

Chronic tubulointerstitial diseases — commonly caused by analgesics, calcineurin inhibitors, lithium, and proton pump inhibitors (which have been associated with both acute and chronic interstitial nephritis); whenever interstitial nephritis suspected, removal of offending agent important as first course of therapy; if, after removal of suspected agent, renal disease continues to progress or does not improve, biopsy may be recommended; corticosteroids may be used in nonresolving or worsening cases in attempt to decrease any element of acute inflammation

Findings: urine eosinophils, if present, may be helpful in diagnosis, but diagnostic sensitivity and specificity for acute drug-induced interstitial nephritis quite low; presence of other systemic symptoms (*eg*, rash) may or may not be present; occasionally, biopsy helpful for unexplained acute kidney injury; high degree of suspicion required when considering drug-induced interstitial nephritis

Key points for tubulointerstitial diseases:

1. A high degree of suspicion is required in investigating patients with either acute or chronic kidney disease of unknown etiology.
2. Characteristic clinical manifestations that could be clues to tubulointerstitial disease are decline in GFR, evidence of proximal tubular damage or elements of Fanconi syndrome, the presence of non-anion gap metabolic acidosis, decrease in urine concentrating ability, low-grade proteinuria, and, if needed, findings from a renal biopsy.
3. Numerous etiologies can lead to chronic tubulointerstitial nephritis; these include autoimmune, toxic, hereditary, and infection-related causes. Medication-related causes are a primary etiology in many patients; a high degree of suspicion is required in those cases.
4. Proton pump inhibitors, a drug class that is highly prescribed for patients, can be associated with both acute and chronic tubulointerstitial nephritis. In patients with unexplained renal failure, those drugs should be stopped and the patient monitored for improvement or worsening of kidney function after discontinuation.

Suggested Reading

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Diagnosis and Management of Glomerulonephritis

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Overview: glomerulus, basic filtering unit of kidney; consists of tuft of capillaries formed by branching of afferent arterial, supported by structural matrix including mesangial cells; each kidney has ~1 million glomeruli; major functions include filtering blood and producing ultrafiltrate (urine); numerous primary and secondary diseases can affect glomerular structure; diseases classified typically as either nephrotic or nephritic; nephrotic diseases characterized predominately by leakage of plasma proteins into urine; nephritic syndromes, or glomerulonephritis, more inflammatory, entire glomerulus may be inflamed, leading to passage of not just plasma proteins but also erythrocytes and white blood cells (WBCs) through glomerulus and into renal tubule; these classifications somewhat arbitrary; actual manifestations of glomerular diseases can cross over between being nephrotic and nephritic, can change over time as well; glomerular diseases can be primary, idiopathic, hereditary, or secondary; secondary to infection (*eg*, human immunodeficiency virus [HIV], hepatitis C); secondary to autoimmune disease (*eg*, systemic lupus erythematosus, cryoglobulinemia); glomerular disease suspected if proteinuria (especially >3.5 g/day), as well as hematuria (especially if red blood cell [RBC]casts); in most cases, confirm via renal biopsy

Nephrotic syndrome: >3.5 grams per 24 hrs excretion of urine protein, or urine protein/creatinine ratio >3500 mg/g; patients typically also manifest hypoalbuminemia, edema, hyperlipidemia; may or may not exhibit all features; other complications include hypercoagulability, may be related to urinary loss of anticoagulant proteins (*eg*, protein C, antithrombin III); increased propensity for infection, especially younger patients, possibly due to urinary loss of immunoglobulins; nephrotic syndrome can be primary or idiopathic, or secondary to systemic diseases; diabetic nephropathy most common etiology of secondary nephrotic syndrome; *most common causes of nephrotic syndrome other than diabetes* — minimal change nephropathy in children, membranous nephropathy or focal segmental glomerulosclerosis (FSGS) in adults; in Caucasian patients, membranous nephritis more common, in African American patients, FSGS more common

Initial evaluation: serum chemistries to assess renal function, liver function tests, serum protein measurements to assess degree of hypoalbuminemia, urinalysis with urine protein quantification, and likely renal biopsy; exclude secondary causes related to systemic disease, infection, malignancy, or medication; test for diabetes (*eg*, hemoglobin A1c); limited screening for collagen vascular disease, guided by presence or absence of systemic symptoms; kidney biopsy required for definitive diagnosis, prognosis, and defining treatment; elevated lipid levels should be treated aggressively with statin drugs; prophylactic anticoagulation controversial; patients with risk factors for thrombotic events (*eg*, serum albumin level <2.0 g/dL or <2.8 g/dL for patients with membranous nephropathy) may benefit if low risk of prophylactic anticoagulation; little scientific evidence to support

Nephritic syndrome: associated with inflammation of glomerular tuft, leading to hematuria, proteinuria, and WBCs in urine; *hematuria often has characteristic features* — RBCs appear crenated (*ie*, dysmorphic); presence of RBC casts (erythrocytes embedded in Tamm-Horsfall protein [THP] of kidney, then excreted in urine, signifies glomerulonephritis; *proteinuria* — variable, from few hundred mg/day up to nephrotic range; often higher degree of hypertension when presenting with abnormal renal function than in nephrotic syndrome patients

3 general classifications: 1. patients have anti-glomerular basement membrane antibodies (anti-GBM Ab); 2. patients have pauci-immune glomerulonephritis (also termed antineutrophil cytoplasmic antibodies [ANCA]-positive vasculitis), in which necrotizing glomerulonephritis occurs and has few small immune deposits; 3. immune complex disease (*eg*, lupus nephritis or poststreptococcal glomerulonephritis); categories can be distinguished clinically by measuring serum complement levels, typically normal in anti-GBM Ab or pauci-immune glomerulonephritis; with immune complex diseases, complement levels tend to be depressed, exception IgA nephropathy, which can exhibit normal complement levels

3 major clinical presentations: 1. acute glomerulonephritis; possibly abnormal renal function, possibly hypertension, abnormal urine sediment; 2. more ominous presentation, rapidly progressive glomerulonephritis; renal function deteriorates quickly; characteristic renal biopsy finding of "crescents" in glomerular tuft; 3. chronic, slowly progressive glomerulonephritis

Conditions Associated with Nephrotic Syndrome

FSGS: accounts for ~25% of adult idiopathic nephrotic syndrome; more common in patients of African

American descent; classified as primary or secondary; primary form may be idiopathic or due to genetic mutations in foot process cells (*ie*, podocytes); secondary causes include hyperfiltration injury, typically seen in obese patients or patients with decreased renal mass relative to body size; other secondary causes include direct podocyte injury from infections (*eg*, HIV) or medications (*eg*, pamidronate, interferon)

Clinical manifestations: similar to general nephrotic syndrome; additionally, patients have hypertension, some degree of microscopic hematuria, abnormal renal function; most serological tests for secondary diseases negative; complement levels within normal limits; diagnosis by renal biopsy, demonstrates segmental scars present in some, but not all, glomeruli; may also be various degrees of tubular atrophy and fibrosis, which correlate with renal function

Treatment and prognosis: unclear, especially if idiopathic; typically, few patients enter spontaneous remission, thus therapy usually indicated; therapeutic regimens include corticosteroids and/or calcineurin inhibitors; with therapy, 40% to 50% of patients achieve complete or partial remission; remission improves prognosis for renal function; FSGS has predilection for reappearing in transplanted kidney in ~20% to 30% of cases; if secondary cause suspected, treat etiologic agent; patients with obesity-related FSGS demonstrate decreases in urine protein and improved prognosis with weight loss; *important aspect of treatment of all proteinuric renal diseases, including glomerular diseases* — "background" treatment with angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB); can be effective in decreasing degree of urinary protein wastage and can improve renal prognosis

Membranous nephropathy: most common cause of idiopathic nephrotic syndrome in adult Caucasian patients; primary or idiopathic and secondary forms; secondary form associated with infection (*eg*, hepatitis B, malaria, syphilis), systemic lupus erythematosus (*ie*, class V lupus erythematosus glomerulonephritis), medications, and malignancies (especially lymphoma); in past 10 yrs, idiopathic membranous nephropathy linked with presence of circulating antibody directed to specific podocyte surface antigen phospholipase A2 receptor (PLA2R); measurement of serum levels of this antibody and its identification on renal biopsy can be useful in both diagnosing membranous nephropathy as well as following patients (decreases in serologic titer predicts remission)

Clinical manifestations: similar to other forms of nephrotic syndrome; additionally, thromboembolic events more common, especially renal vein thrombosis; furthermore, up to one-third of adult patients have an underlying occult malignancy; recommended that patients have age-appropriate cancer screening; diagnosis by renal biopsy supplemented by finding PLA2R antibodies; one-third of patients enter spontaneous remission within first ~6 months to 12 months after diagnosis

Treatment: milder forms of membranous nephropathy with normal renal function and proteinuria may be managed with ACE inhibitor or ARB; not unreasonable to attempt conservative management for several months to see if condition improves; if no improvement after period of watchful waiting, for those with more severe disease, or for those who worsen during conservative management, specific immunosuppression should be considered; many different immunosuppressive regimens; most include a glucocorticoid with either cyclophosphamide, calcineurin inhibitor, mycophenolate mofetil and, most recently, rituximab (anti-B cell antibody); for more refractory cases, newer therapy utilizing adrenocorticotrophic hormone (ACTH) may be used; if secondary, treatment of underlying condition recommended (if successful, glomerular disease will likely improve)

Minimal change disease (MCD): most common cause of idiopathic nephrotic syndrome in children; seen in ~10% of adults, especially elderly; primary and secondary causes; *secondary causes* — medications (*eg*, lithium, nonsteroidal anti-inflammatory drugs [NSAIDs], interferon), malignancies (especially Hodgkin lymphoma)

Clinical manifestations: similar to other forms of nephrotic syndrome, except edema usually more profound; urine protein levels can be extreme (≥10 g/day); in adults, some patients may present with significant azotemia and renal failure; urine sediment usually benign, with absence of hematuria or other cellular elements; serological tests for systemic diseases usually negative; *diagnosis* — renal biopsy; under light microscopy, normal immunofluorescence, but on electron microscopy, podocyte foot processes effaced (*ie*, "run together as single unit"), characteristic of proteinuric renal diseases

Treatment: most patients treated for 2 mos to 4 mos with high-dose glucocorticoids, often leading to remission; however, relapse can commonly occur; treatments for relapse include cyclophosphamide, calcineurin inhibitors, mycophenolate mofetil, and rituximab

Diabetic nephropathy: leading cause of end-stage kidney disease in United States, accounting for 40% to 50% of patients with frank kidney failure; older patients, those with worse glycemic control, of certain ethnic groups (Native American, Mexican American, or African American), as well as those with hypertension, who smoke, and have family history of kidney disease, have higher rate of progression; degree of urine albumin one of biggest predictors of progression to worsening kidney failure; patients who have macroalbuminuria or urine albumin-to-creatinine ratio (UACR) >300 mg/g of urine have higher risk of progressive kidney disease

Pathology: typically, all compartments of kidney affected histologically; within glomerulus, thickening of basement membrane (GBM), followed by nodular sclerosis (Kimmelstiel-Wilson lesion), leads to global sclerosis of glomerular tuft along with tubular fibrosis and atrophy; can also see significant small-vessel arteriosclerosis on biopsy

Clinical manifestations: albuminuria typically beginning in mean of 5 yrs to 15 yrs from diagnosis in type 1 diabetic patients; more variable in type 2 diabetic patients; ~30% of patients with diabetes develop microalbuminuria (*ie*, UACR 30-300 mg/g); more overt nephropathy occurs when UACR >300 mg/g, typically seen after longer duration of diabetes, ~10 yrs to 15 yrs for type 1, more variable rate for type 2; patients with high UACRs at high risk for progression to end-stage kidney disease

Diagnosis: renal biopsy not usually needed; annual testing of urine for albumin recommended in patients with

diabetes; renal biopsy recommended only if additional systemic disease suspected to be causing lesion

Conditions Associated with Nephritic Syndrome

Anti-GBM Ab disease (anti-GBM disease): autoimmune disease characterized by development of antibodies, typically immunoglobulin G (IgG), directed against type 4 collagen present in basement membrane of glomeruli; upon binding to glomerular basement membrane, these antibodies incite significant inflammatory response that severely damages GBM; leads to presence of RBCs (typically dysmorphic), RBC casts, WBCs, and protein in urine; also leads to proliferative, inflammatory, and often rapidly progressive glomerulonephritis with presence of "crescents" on biopsy; kidney failure can occur within weeks of diagnosis; in some cases, same process will occur in basement membrane of pulmonary capillaries, leading to diffuse alveolar hemorrhage; if both diffuse alveolar hemorrhage and renal manifestations, Goodpasture syndrome; anti-GBM disease typically infrequent, probably <3% of all causes of nephritic syndrome, <15% of cases of rapidly progressive glomerulonephritis

Diagnosis: typically made if high titers of anti-GBM antibody levels; renal biopsy demonstrates linear basement membrane staining of pathogenic antibodies

Treatment and prognosis: treat aggressively to save renal function; therapy includes high-dose intravenous corticosteroids initially, followed by cyclophosphamide; for patients presenting with more severe disease, including those presenting with significant elevations in serum creatinine as well as diffuse alveolar hemorrhage, daily plasmapheresis to rapidly remove circulating anti-GBM antibodies; prognosis poor, likelihood of renal recovery low in patients presenting with dialysis-requiring acute kidney injury due to rapidly progressive glomerulonephritis from anti-GBM disease

Pauci-immune glomerulonephritis: microscopic small-vessel vasculitis; can affect kidneys as well as other organ systems; within kidney, leads to necrotizing lesions that typically have few, or very little, immune deposits on renal biopsy; patients may or may not have systemic symptoms, or may have renal-limited vasculitis

3. general forms of systemic vasculitis: 1. disease formerly known as Wegener granulomatosis (now known as granulomatosis with polyangiitis [GPA]); typically associated with positive ANCA serologies, specifically associated with antibodies to proteinase 3 (PR3 ANCA); 2. microscopic polyangiitis (MPA); typically, similar to GPA except no granulomas and serologic test primarily shows positive myeloperoxidase (MPO) ANCA antibodies; 3. formerly Churg-Strauss disease (now known as eosinophilic granulomatosis with polyangiitis); typically associated with asthma, pulmonary infiltrates, and eosinophilia

Clinical manifestation: often, patients with any of these forms will have nonspecific systemic symptoms (*eg*, fever, myalgia, fatigue, poor appetite); other signs and symptoms, including pulmonary disease or skin manifestations (*eg*, leukocytoclastic vasculitis) may be present

Diagnosis: combination of renal biopsy and serologic testing for ANCA antibodies; ~10% of patients have no ANCA antibodies; false-positive ANCA serologies can also occur, especially in conditions such as inflammatory bowel disease

Treatment and prognosis: aggressive treatment needed; prognosis often poor; usually combination of glucocorticoids, cyclophosphamide, with or without plasmapheresis, as initial treatment; plasmapheresis reserved usually for patients with diffuse alveolar hemorrhage or more severe disease, including dialysis-requiring renal failure; other therapies include rituximab, which can be considered for mild and moderate disease and has better side-effect profile than cyclophosphamide; all therapies followed with maintenance therapy, usually combination of either azathioprine, mycophenolate mofetil, or methotrexate

Immunoglobulin A (IgA) nephropathy: frequent cause of chronic glomerulonephritis, especially in East Asia; tends to occur more frequently in men; notable for IgA-forming immune complex formations in kidney; also form of IgA systemic vasculitis (Henoch-Schönlein purpura) that can involve other organ systems; in adults with IgA nephropathy, asymptomatic microscopic hematuria with or without low degrees of proteinuria typical manifestation; proteinuria variable; also syndrome associated with IgA nephropathy in which patients demonstrate episodic gross hematuria in presence of upper respiratory tract infection (synpharyngitic nephritis or synpharyngitic hematuria)

Clinical manifestation: IgA nephropathy can have protean manifestations in kidney, from mild disease to very severe, rapidly progressive, crescentic glomerulonephritis; no serological tests available to diagnose IgA nephropathy; kidney biopsy required for diagnosis, prognosis, and therapeutic information

Treatment: tends to be chronic disease; prognosis very good for many patients, especially if proteinuria <1 g/day and renal function normal; vast majority of patients will have nonprogressive disease; those with higher degrees of proteinuria (>1 g/day), hypertension, presenting with kidney dysfunction, and who have tubular interstitial damage and scarring on biopsy carry worse prognosis, in which case glucocorticoids should be considered; all patients with proteinuria should be treated with either ACE inhibitor or ARB

Lupus nephritis (systemic lupus erythematosus–associated kidney disease): *classification schemes for lupus* — class I, minimal mesangial lesion, no real clinical findings; class II, mesangial proliferative lupus nephritis with mild kidney disease, some degree of hematuria, and minimally active urine sediment; renal function typically normal; class III, focal proliferative lupus nephritis; on biopsy, <50% of glomeruli involved; urine sediment tends to be active, with higher degrees of proteinuria, hematuria, dysmorphic RBCs, RBC casts; hypertension usually present, abnormal renal function follows as well; class IV, more diffuse proliferative lesion, with >50% of glomeruli involved by disease process; kidney involvement much more severe, hypertension nearly always present, along with heavy proteinuria, and abnormal renal function; class V, membranous glomerulonephritis, similar to membranous glomerulonephritis that leads to predominantly nephrotic syndrome presentation; class VI, advanced sclerotic lesion leading to end-stage renal disease; >90% of glomeruli fibrosed or sclerotic

Pathology: immune deposit disease
Diagnosis: serologic tests include antinuclear antibodies and anti — double-stranded DNA antibodies, typically positive; both C3 and C4 complement levels depressed, signifying activation of classic complement pathway; kidney biopsy required to classify form of lupus nephritis and guide prognosis and therapy
Treatment: depends upon class of lesion; typically, patients with class I or II require prednisone or watchful waiting and conservative management; patients with class III and IV benefit from aggressive combination immunosuppressive therapy (*eg*, prednisone, cyclophosphamide, and/or mycophenolate mofetil); in more severe cases, plasmapheresis may be added; patients with class V treated as for membranous nephropathy

Infection-related glomerulonephritis: also classic immune complex–related glomerulonephritis; *poststreptococcal glomerulonephritis classic presentation* — glomerulonephritis typically occurs ~1 wk after streptococcal infection; caused by immune complexes directed against pathogenic antigens from bacteria; rare now; more commonly now, glomerulonephritis after staphylococcal or gram-negative infections;
Pathology: antigen in immune complex from infectious agent, typically deposits in subepithelial area within glomerulus; leads to complement activation and subsequent recruitment of inflammatory cells and mediators leading to glomerulonephritis
Clinical manifestation: patients present with acute nephritic syndrome; most commonly, as opposed to poststreptococcal glomerulonephritis, patients with staphylococcal-associated glomerulonephritis often have ongoing infection at time of development of nephritis
Diagnosis: made clinically; patients have active infection, nephritic sediment, may have hypertension, and abnormal renal function; typically, complement levels (usually C3) depressed, signifying activation of alternate complement pathway; renal biopsy may be needed, since patients often present diagnostic challenges, often quite ill with multiple possible renal insults; biopsy demonstrates proliferative glomerulonephritis, possibly with C3 deposition staining
Treatment and prognosis: dependent on treatment of underlying infection; minimal data to show that immunosuppressive therapy has role in treatment; prognosis can be poor (nearly 50% of patients experience end-stage kidney disease), especially if underlying infection cannot be controlled quickly and effectively

Manifestations of Monoclonal Gammopathies Within Kidneys or Renal Tubules

Overview: monoclonal antibody production by lymphocytes or plasma cells can lead to many different kidney disorders; can predominately involve glomerular or tubular structures; in recent years, noted that many glomerular tubular disorders associated with monoclonal gammopathy may not completely fulfill criteria for lymphoma or overt myeloma; thus, known as monoclonal disorders of renal significance; recommendation to treat many of these conditions as myeloma or lymphoma
Kidney manifestations: can include proteinuria, full nephrotic syndrome, tubular dysfunction (*eg*, Fanconi syndrome), as well as renal failure
Diagnosis: rests on finding monoclonal protein; serum and urine protein electrophoresis, as well as serum free light-chain ratio used for diagnosis; diagnosis supplemented with renal biopsy as manifestations in kidney cannot be easily predicted clinically, biopsy needed to determine particular form of renal dysfunction present
Treatment: overall management focused on treatment of underlying monoclonal disorder, should be done in conjunction with hematologist; therapy for renal disorder largely supportive, with hope that treatment of underlying monoclonal disease leads to improvement or stabilization of renal function

Types: one classification criteria, assess pattern of immune deposition; monoclonal proteins can either deposit in organized fashion or in nonorganized deposits; organized deposits include amyloid light-chain (AL) amyloidosis, immunotactoid glomerulonephritis, fibrillary glomerulonephritis, and cryoglobulinemic glomerulonephritis; nonorganized deposits called monoclonal deposition disease or light- or heavy-chain deposition disease, depending upon particular form of protein found; irrespective of pattern of deposition, treatment essentially same, relies on treatment of the underlying malignancy

Key Points

1. Nephrotic syndrome characterized by high degrees of urine protein excretion >3500 mg in 24 hrs; diabetes mellitus most common cause of nephrotic syndrome, followed by conditions such as MCD (more prevalent in children) and membranous nephropathy and FSGS (more common in adults)
2. Nephritic syndromes associated with glomerular inflammation, hematuria, abnormal renal function, hypertension, and variable degrees of proteinuria; common causes of nephritic syndrome include immune-complex disorders, pauci-immune glomerulonephritis, and anti-GBM disease
3. Renal biopsy required in nearly all glomerular diseases to give accurate diagnostic, and therapeutic, as well as prognostic, information
4. Early and aggressive therapy with immunosuppressive medications for both nephrotic and nephritic syndromes have improved prognosis for patients

Suggested Reading

Cavanaugh C et al: Urine sediment examination in the diagnosis and management of kidney disease: core curriculum 2019. *Am J Kidney Dis*. 2019;73(2):258-72; **Couser WG:** Pathogenesis and treatment of glomerulonephritis-an update. *J Bras Nefrol*. 2016;38(1):107-22; **Kidney Disease Improving Global Outcomes.** Clinical practice guideline for glomerular disease. https://kdigo.org/guidelines/. Accessed February 20, 2019; **Liebeskind DS:** Nephrotic syndrome. *Handb Clin Neurol*. 2014;119:405-15.

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Nephrology

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Objectives: discuss common inflammatory and obstructive urinary conditions including urinary tract infections (UTIs), pregnancy-related issues, urinary obstruction, kidney stones

UTIs: categorized anatomically (upper or lower tract) or by clinical complexity; urethritis and cystitis lower-tract diseases; kidney infections, pyelonephritis, prostate upper-tract disease; infections simple or complex; simple infections limited to bladder of nonpregnant women of childbearing age with no comorbidities or urologic abnormalities; UTIs in most others (men, children, postmenopausal women) not simple; these infections have factors that interfere with normal host defenses (*eg*, obstruction, retention, immunosuppression, transplantation, pregnancy, foreign bodies including stones, catheters); UTI in men always complex

Recurrence: tremendous burden of UTIs high rate of recurrence (defined as 2 uncomplicated infections in 6-month period or 3 infections within 1 year); recurrent UTIs can be reinfections with new or same organism; relapse may not represent failed treatment; may be from organisms that develop protective biofilm, so that even adequate antibiotics cannot completely eliminate them

Asymptomatic bacteriuria: isolation of bacteria from normally sterile genitourinary (GU) tract but without any signs/symptoms of infection; other than pregnant patients and those going for invasive GU procedure (*eg*, transurethral resection of the prostate [TURP], cystoscopy), patients should not be tested or treated for UTI; do not send asymptomatic patient urine for culture, you'll get positive result for infection you shouldn't be treating (*eg*, don't treat kidney transplant patient with asymptomatic bacteriuria); 3 randomized control trials currently enrolling patients to test if any advantage to treating asymptomatic bacteriuria in transplant patients; so far, no advantage in either rejection rates, graft survival, or patient satisfaction; don't treat HIV patients with asymptomatic UTI; current recommendations say if no symptoms localized to urinary tract (pain, dysuria, burning, urgency, incontinence, stranguria, pubic tenderness [really only physical exam finding of cystitis]), don't test and treat UTI; if asymptomatic bacteriuria treated, patient can get colonized with highly resistant bacteria, ultimately resulting in invasive and difficult-to-treat infection

Epidemiology: common; ~10% of women have UTI each year and up to 50% have recurrence; elevated UTI risk begins with onset of sexual activity; some claim risk decreased by voiding after sex, but no evidence for this claim; UTIs rare in men age <50 yrs; in infants, UTIs more common in males than females; *other risk factors* — anal sex associated with male UTI; HIV patients with CD4 counts <200; uncircumcised males

Microbiology: *primarily gut flora that colonize periurethral area ascending into bladder* — *Escherichia coli* primary cause of UTIs, cause 80% simple UTIs; *Staphylococcus saprophyticus* 5% to 10%; with complicated UTIs, broader range of bacteria, in addition to *E coli* and *S saprophyticus*, also *Proteus*, *Enterococcus*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Pseudomonas*, *Serratia*, yeast; UTIs generally gram-negative infections, gram-positive cocci less common, except for *S saprophyticus* and *S epidermidis* in patients with catheters; *S aureus* suggests bacteremic kidney infection, not typical cause of classic ascending infection; *urine naturally antibacterial* — high urea content, low pH, high osmolality; all create hostile environment for bacteria; bladder has host defenses; bladder secretes interleukins 6 and 8, which bring polymorphonuclear leukocytes to interact with bacteria

Diagnosis: symptoms include dysuria, urgency, hematuria, suprapubic tenderness; women with recurrent UTIs can reliably self-diagnose; if already had UTI, they know what it feels like; studies show no difference in symptom score, patient satisfaction, or outcome between diagnosing these over phone vs having patient come into office

Pyelonephritis: presents with costovertebral angle tenderness, with or without fever; patient appears ill, very uncomfortable, may have tachycardia; infants, if fever, have failure to thrive

Acute prostatitis: severe systemic illness; high fever, bacteremia, often involves urinary obstruction; chronic bacterial prostatitis may resemble acute cystitis relapse in older men; if man with recurrent UTIs can't seem to clear infection, think prostatitis

Diagnosis: don't need culture for simple cystitis; patients reliably self-diagnose so start treating; for complex UTI, get urine culture because of wide range of causative bacteria; need to know which one to treat for; marker of positive culture 10^5 colony-forming units (CFU)/mL; in simple cystitis, ~1000 CFU/mL, in patients with classic symptoms, 100 CFU/mL diagnostic; on dipstick, nitrates and leukocyte esterase most accurate indicators of acute, uncomplicated cystitis in symptomatic women; absence of pyuria in symptomatic patient reliable for excluding UTI; if suspect disease not UTI, urinalysis enables elimination

of UTI from differential; *nursing home patients* — many symptoms blamed on phantom UTIs; UTI not cause of confusion or falls in elderly patients; presence of pyuria, foul-smelling urine, bacteria, hematuria not indications for use of antibiotics in absence of localizing signs or symptoms

Treatment: usually short course of antibiotics; use agents that get good concentration in urine; first-line agents are trimethoprim/sulfas 1 double-strength tablet twice daily for 3 days; some communities have high resistance rates (>20%), so avoid this drug in that situation; other first-line agents nitrofurantoin (100 mg twice daily for 5 days) or fosfomycin (1 g, 1 dose); quinolones good but because of side-effect profile, not recommended as first-line agents; beta-lactams acceptable but not as effective, require 7-day (amoxicillin/clavulanic acid or cefpodoxime) to 10-day (cefdinir) course rather than 1- to 5-day course for first-line agents; pyelonephritis generally needs IV therapy, but maybe can get away with oral quinolones for some low-risk patients (with minor symptoms, no comorbidities)

UTIs in pregnancy: relatively common (2%-8% of pregnancies); need to treat asymptomatic bacteriuria, transitions to pyelonephritis in 20% to 30%; decreased urethral tone from progesterone, decreased ureteral peristalsis, thus vesicoureteral junction more incompetent, making it easier for bladder infections to ascend; obstruction from expanding uterus, increased urinary stasis, compromised ureteric valves, vesicoureteral reflux all facilitate bacterial colonization and ascending infection; maternal UTI associated with low birth weight, premature delivery, neonatal death; pregnant women should be screened at very first prenatal visit for asymptomatic bacteria; American College of Obstetricians and Gynecologists recommends second screening in third trimester; US Preventive Services Task Force recommends single screening at 12 to 16 wks; recommend urine culture, not urinalysis or dipstick

Treatment: nitrofurantoin, cephalosporins, fosfomycin acceptable treatment options in pregnancy; sulfonamides valid option in first and second trimesters, but during third trimester, increased risk for kernicterus, especially in preterm infants; fluoroquinolones and tetracyclines toxic to fetus; patients should get repeat culture after treatment to confirm sterile urine; if recurrence develops, place patient on daily suppressive antibiotics for rest of pregnancy

Kidney and pregnancy: kidney has impressive plasticity during pregnancy and behavior changes during pregnancy; grows in length by 1 to 1.5 cm (10% to 15% increase); represents increase in vascular size and interstitial volume but not number of nephrons; dilation of collecting system occurs, can resemble hydronephrosis; peaks at ~28 weeks with ultrasound evidence of hydronephrosis in ~2/3 of pregnant women; increased ureteral volume represents 200 to 300 mL of urine, leading to urinary stasis, increasing risk for pyelonephritis; thought to be effect of progesterone, but recent data show result of mechanical obstruction; right-sided hydronephrosis predominates; *blood pressure (BP)* — pregnant women have drop in BP of ~10 mm Hg, despite dramatic increase in renin, angiotensin, and aldosterone (normally associated with increases in BP); pregnancy causes renin-angiotensin-aldosterone resistance, probably because of increased progesterone levels; preeclampsia likely occurs at restoration and normalization of renin-angiotensin-aldosterone system response; once patient re-responds to these hormones normally, increase in BP; aldosterone levels very high; upper limit of normal aldosterone 14 ng/dL, but in pregnancy, increases to 80-100 ng/dL, probably enables women to increase total body fluid; drop in BP due to decrease of total peripheral resistance; *kidney function* — glomerular filtration rate (GFR) increases by 50%; creatinine falls to 0.5 to 0.7 mg/dL and uric acid 2 to 3 mg/dL during pregnancy; estimates of renal function from routine lab studies with Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration equation not validated in pregnancy (they underestimate GFR in pregnancy); 24-hr urine collections for creatinine clearance only way to measure GFR in pregnant women; pregnant women have electrolyte changes, get glucosuria, does not mean diabetes; can occur with normal serum glucose; ability to reabsorb glucose in proximal tubule decreased; serum sodium concentration decreased due to reset osmostat; normal sodium drops to 134 mEq/L and serum osmolality to 270 mmol/kg/L, driven by increased antidiuretic hormone activity; women develop respiratory alkalosis; normal bicarbonate level drops from 24 to 28 mEq/L to 18 to 20 mEq/L; patients do not have nonanion gap metabolic acidosis, respiratory alkalosis driven by progesterone

Preeclampsia: most common glomerular disease in world, 5% to 7% of all pregnancies; when untreated can cause seizures (eclampsia), liver rupture, stroke, pulmonary edema, kidney failure can be lethal; can cause fetal growth restriction and preterm birth (either from spontaneous preterm labor or from treating preeclampsia by inducing labor); children born to mothers with preeclampsia have increased risk for bronchopulmonary dysplasia and cerebral palsy; probably most important hypertensive disorder of pregnancy; can occur at or after 20 weeks, BP changes before that time not preeclampsia; proteinuria no longer criterion for diagnosis; diagnosis requires new onset or increased severity of hypertension (HTN) (*ie*, BP >140/90 mm Hg) after 20 weeks' gestation, combined with evidence of end organ damage, *eg*, proteinuria >300 mg/d, renal failure, liver involvement, neurologic changes (*eg*, visual disturbances, headache, encephalopathy), hematologic consequences like low platelets, and uteroplacental dysfunction (can result in fetal growth restriction); since proteinuria no longer required for preeclampsia, we divide disease into proteinuric and nonproteinuric preeclampsia; *severe preeclampsia* — HELLP (microangiopathic **h**emolytic anemia, **e**levated **l**iver enzymes, **l**ow **p**latelets) syndrome; can be accompanied by severe manifestations (*eg*, kidney failure, stroke, blindness from vasoconstriction in occipital lobe or retinal detachment, disseminated intravascular coagulation, hepatic rupture, pulmonary edema, seizures)

Risk factors for preeclampsia: history of preeclampsia, pregnant with twins, preexisting HTN, preexisting diabetes, or any type of kidney disease, including

donating kidney; any patient with autoimmune disease (*eg*, lupus or antiphospholipid antibody syndrome); those at moderate risk include first pregnancy, obesity, first-degree relative (mother or sister)who had preeclampsia, blacks, low socioeconomic status, aged >35 yrs, previous adverse pregnancy outcome, infant with low birth weight or small for gestational age or prematurity, and >10 yrs since last pregnancy; different guidelines for high and moderate risk

Treatment and prevention: all those at high risk should start low-dose aspirin after 20 weeks to prevent preeclampsia; not powerful but measurable effect; those at moderate risk, discuss aspirin use to make decision; evidence does not support aspirin use for entire moderate risk population; some evidence that calcium supplementation may reduce risk for preeclampsia, but seemed to affect only women with diet low in calcium; once patient gets preeclampsia, delivery of placenta only cure; can use magnesium to lower risk for seizures and to treat seizures if occur; after clearing preeclampsia; subsequent risk for cardiovascular disease and kidney disease, *eg*, need for dialysis or kidney biopsy

Mechanism: fundamental problem believed to be incomplete remodeling of uterine spiral arteries, resulting in placental ischemia; ischemic placenta releases anti-angiogenic factors (*eg*, soluble FMS-like tyrosine kinase 1 [sFLt1] and soluble endoglin), which cause vasoconstriction; potential promising new treatment; data show specialized plasmapheresis to remove sFLt1 may ameliorate effects of preeclampsia

Other hypertensive disorders of pregnancy: if have chronic HTN before pregnancy, will have HTN during pregnancy, which increases risk for preeclampsia; patients can have chronic HTN and have superimposed preeclampsia; gestational HTN occurs late in pregnancy (usually at ≥36 wks) but does not involve end organ damage or proteinuria and resolves postpartum; those patients have risk for future essential HTN; treating HTN in pregnancy, be conservative; target BP <160/105 mm Hg; women who have catastrophic outcomes (*eg*, stroke) BPs were >160/110 mm Hg; want systolic 120 to 160 mm Hg, diastolic 80 to 105 mm Hg; be careful, since every 10 mm Hg reduction in systolic BP results in 145 g reduction in birth weight; do not use angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), cause teratogenicity; can use calcium-channel blockers, but need to be careful if patient on magnesium for preeclampsia or eclampsia (can cause profound hypotension); labetalol beta blocker to use; atenolol has been associated with decreased fetal growth; alpha-methyldopa has long history of safety in pregnancy, but not that effective as single agent; hydralazine safe but not effective as single agent, needs pairing with beta blocker; diuretics safe, but late in pregnancy, can trigger premature labor

Acute kidney injury in pregnancy: preeclampsia most common cause; hemolytic-uremic syndrome (HUS) seen in pregnancy, can be difficult to differentiate from preeclampsia; preeclampsia has increased liver enzymes, abnormal clotting factors, less in HUS; acute tubular necrosis in pregnancy, high risk of causing cortical necrosis; patients unsatisfying recovery from kidney injury, significant residual decrease in kidney function; if patient gets kidney disease in pregnancy, can be more severe

Cystic diseases of kidney: fluid-filled cavities lined by epithelial cells derived from tubules of collecting duct; acquired cysts common, can be single or multiple; increase in frequency with age, rarely clinically meaningful; low potassium can cause cystic kidney disease

Autosomal dominant polycystic kidney disease (PKD): most common, lethal autosomal dominant disease; affects 1 in 500 births; characterized by development and progressive enlargement of renal cysts, leading to chronic renal failure and dialysis dependence by late middle age; 2 types of adult-onset PKD, types 1 and 2; PKD type 1, polycystin-1 on chromosome 16; type 2, less severe phenotype, polycystin-2 on chromosome 4; genes encode large proteins, can have many different individual mutations, many phenotypes for PKD 1; anything affecting polycystin-1 causes PKD 1, no specific genetic defect to look for; anyone in family has same genetic defect but varies from family to family

Diagnosis: genetic tests not reliable for diagnosis; ultrasound standard for diagnosis, though computed tomography (CT) and magnetic resonance imaging (MRI) can resolve small cysts for diagnosis at younger age; cysts unusual in young people, but risk increases with age; as people age, *sensitivity* of ultrasound rises (can rule out diagnosis) but *specificity* falls due to acquired cysts; to counter fall in specificity, definition requires more cysts and bilaterality as you get older; consensus definition for persons aged 15 to 39 yrs, need ≥3 cysts, 81% sensitivity in persons aged 15 to 29 yrs, 96% sensitivity in persons aged 30 to 39 yrs; ultrasound 97% specific at ruling out disease; no cysts by age 29 yrs, 97% chance they do not have disease; by age 39 yrs, no cysts, 94% specific; at age 40 to 59 yrs, definition changes to confirm diagnosis, >2 cysts in each kidney to rule out cysts, 90% sensitive, 94% specific; if determining if family member can donate kidney, use MRI, can differentiate cysts from parenchyma without need for contrast, can also be used to accurately track kidney volume; if <5 cysts by MRI, rule out disease in person aged 16 to 40 yrs; kidney failure most prominent symptom of autosomal dominant PKD

Extrarenal manifestations: liver cysts (usually asymptomatic but sometimes pain or liver dysfunction); pancreatic cysts (usually asymptomatic); ovarian cysts not associated with autosomal dominant PKD, but cysts in seminal vesicles are (rarely cause infertility); vascular weakness, which can present as intracranial berry aneurysms; cervicocephalic artery dissections, coronary artery aneurysms; *berry aneurysms* — occur in ~6% patients without family history of PKD and in 16% of patients with family history; per current recommendations, generally do not screen for berry aneurysms in asymptomatic patients without personal or family history of intracranial aneurysms or subarachnoid hemorrhage; can screen if patient in high-risk occupation (*eg*, pilot, bus driver) or undergoing major surgical procedure where may have hemodynamic instability, treat aneurysm before

procedure if possible; magnetic resonance angiography (MRA) for screening, but if patient symptomatic, severe headache and concern about subarachnoid hemorrhage, CT scan best, more sensitive than MRA

Other manifestations: mitral valve prolapse common (up to ~25% of patients); diverticulosis, diverticulitis, abdominal hernias (especially important for possible candidates for peritoneal dialysis); HTN prominent symptom, begins early in childhood, can be first manifestation of disease; patients may have significant pain (usually abdominal, back, or flank) usually from compression of organs, but could be hemorrhage in cyst, kidney stones, or pyelonephritis, so do workup to determine; *kidney stones* — occur in 20% to 35% of patients, usually uric acid or calcium oxalate stones from urinary stasis and very acidic urine; they can get UTIs and pyelonephritis; renal failure prominent, probably most important symptom; ~50% patients progress to end-stage kidney disease by age 60 yrs; men progress faster than women; renal deterioration not linear; patients can have long period with stable renal function and then hit inflection point and GFR deteriorates rapidly; young, healthier patient still at risk for decline; higher kidney volumes associated with more rapidly declining kidney function

Treatment: most important to control BP, antihypertensive therapy with ACE inhibitor or ARB recommended; combining ACE and ARBs safe, but no advantage; as of 2018, new agent available in US, tolvaptan; studies show it slows progression of autosomal dominant PKD, slows cyst growth and creatinine changes, but not cure; for treatment group, creatinine clearance fell ~2.3 mL/min/y and placebo group fell 3.6 mL/min/y, big difference, but still progress twice as fast as patients typically progress ~1 mL/min/y; tolvaptan first drug for this; ongoing research looking at somatostatin analogs (*eg*, octreotide, lanreotide); *UTIs* — autosomal dominant PKD patients have large volumes, bacteria hide in cysts, typically *Enterobacteriaceae*; if infected cysts (pyelonephritis by definition), require IV antibiotics with good penetration into urine; once patients stabilize, switch to oral antibiotics; need antibiotics that get good penetration into cysts (quinolones and trimethoprim/sulfa); prolonged treatment; several weeks may be required to eradicate infection

Obstructive uropathy: structural or functional interference to normal urine flow anywhere along urinary tract; categorized as acute or chronic, partial or complete, unilateral or bilateral; obstruction increases urine pressure in renal pelvis, leading to dilation of renal tubules; if prolonged, can result in ischemia of distal nephron and distal tubules; distal tubules get rid of acid and potassium; in addition to decreased GFR and kidney function, patients have specific nonanion gap metabolic acidosis and hyperkalemia; with unilateral obstruction, obstructed kidney secretes additional renin, which goes to nonobstructed kidney and increases kidney blood flow and GFR, masking loss of GFR; obstruction causes urinary stasis and predisposes to infection; anyone with infected obstructed kidney or urinary tract requires urgent decompression and resolution of obstruction

Causes: vary with sex and age; older men, may be prostate cancer or benign prostatic hyperplasia; in older women, may be gynecologic malignancies and other anatomic abnormalities along GU tract, prolapse of bladder; in younger adults, stones most common cause; in children, congenital diseases, *eg*, ureteral pelvic junction obstruction, found in ~1 in 1,000-2,000 live births, affects males and females equally

Diagnosis and treatment: suspected because of pain; less pain if chronic obstruction; might cause vomiting and nausea; pain from that kidney stretching and pushing on capsule; diagnosis based on imaging, primarily ultrasound; may miss obstruction in first few days (need to wait for kidney to stretch out); CT scan with and without contrast provide detailed anatomy to assist in surgical correction; mercaptoacetyltriglycine (MAG3) scan, functional test that can demonstrate obstruction and measure clearance on left and right side of body, look for lateralization; if decreased kidney function on obstructed side, may be indication for surgery; if looking at bladder outlet obstruction, best test is postvoid residual; check bladder volume with scan, person urinates, then volume remeasured; bladder should empty 80% of urine post void and volume <50 mL; >100 mL is abnormal, >200 mL is diagnostic of obstruction; careful if using ultrasound bladder scan; ascites can cause false positives, can indicate much larger bladder; once obstruction relieved, patients can experience *postobstructive diuresis* — kidney catching up and getting rid of all accumulated water and solutes; can result in hypokalemia, hypomagnesemia, and hypernatremia; ensure replace electrolytes replaced

Other abnormalities: abnormalities from metabolic (*eg*, diabetes) or neurologic (*eg*, multiple sclerosis) diseases can cause functional bladder abnormalities, which can cause obstruction just as serious as physical obstruction; can cause hydronephrosis, obstruction, and renal failure, without physical blockage, just bad nerves

Kidney stones: 12% of men and 7% of women develop at ≥1 kidney stone; rate increasing; theories include obesity, metabolic syndrome, global warming; used to be male-dominant disease but becoming less so; 50% persons who get kidney stone never get another; other 50% get recurrent kidney stones, so have to figure out why; can make changes in diet and lifestyle to prevent future stones or give medication

Types of stones: need stone analyzed; if patient had previous kidney stones analyzed, each subsequent stone should also be analyzed, can change over time and in response to therapies; 70% are calcium oxalate, 10% calcium phosphate, 10% uric acid, 10% struvite (magnesium ammonium phosphate); many other types of stones but rare; often stones will be mixture of multiple types but 1 type predominant

Diagnosis and workup: most stones, except uric acid stones, seen on plain film; uric acid stones radiolucent; CT scan thin slices without contrast good way to study kidney stones (contrast will camouflage calcium-based stone); CT scan good if looking for cause of flank pain and not stone; ultrasound not as sensitive as CT scan, but good test for recurrent stone formers that are getting exposed to CT scans too often, patients need to refuse CT scan because unnecessary radiation; patient with first stone, get imaging to confirm only 1 stone; if several bilateral stones, patient multiple, recurrent stone former by definition; urinalysis for initial workup,

look for infection; basic metabolic profile, look for hypercalcemia (may suggest hyperparathyroidism); look for hypokalemia or nonanion gap metabolic acidosis indication of renal tubular acidosis, could be cause of kidney stones; if patient recurrent stone former, do everything mentioned above, imaging, do all above plus and check 24- or 48-hr urine collection for calcium, oxalate, uric acid, phosphorus, urine volume, urine citrate, urine pH, urine creatinine; urine calcium, see if patient has hypercalciuria; if excrete excessive calcium, may be associated with osteoporosis; urinary calcium >300 mg (men) or >250 mg (women), patient has hypercalciuria; specific interventions for this; urine oxalate one of prime ingredients for calcium oxalate stones; urine uric acid major cause of uric acid stones; urine volume, kidney stone formers tend to have low urine volumes; one of best and most effective interventions to prevent recurrent kidney stones to ensure patient drinks more water, enough to make 2.5 L/d of urine; urine citrate prevents kidney stones (anti–stone-forming agent); hypocitraturia common metabolic abnormality leading to kidney stones, can supplement with oral citrate; low urine pH risk factor for uric acid stones, high urine pH risk factor for calcium phosphate stones; urine creatinine helps ensure urine specimen collected properly; men make ~20 mg/kg/d creatinine, women ~15 mg/kg/d; if sample much different, inadequate or invalid sample; metabolic syndrome, which may cause increase in stone burden, decreases urine pH, predisposing patient to uric acid nephropathy; *special circumstances* — patients with Roux-en-Y, or biliopancreatic diversion of small bowel, can get significant calcium oxalate stones from enteric hyperoxaluria due to increased fat in distal ileum and colon; fat binds up calcium; same effect as low-calcium diet, leaves oxalate unbound to be absorbed and increases urinary oxalate, increases stones; these patients also have more loose stools and diarrhea, which increases GI output at expense of decreased urinary output, decreasing urine volume and increasing stones; diarrhea leads to metabolic acidosis, which lowers urinary citrate and increases kidney stones; other forms of bariatric surgery, like restrictive procedures, *eg*, gastric banding, no increase in stones; patients with distal or type 1 renal tubular acidosis also get calcium phosphate stones

Treatment: for acute stone, assess size with CT scan; if <5 mm, pass spontaneously 80% to 90% of time; can give patients pain medication, make sure no fever or obstruction, can go for medical expulsion therapy to try to pass that stone; careful with patients with nausea and vomiting, can get volume depleted and develop renal failure; alpha blockers often prescribed although have not performed well on blinded analysis, used to use alpha blockers like tamsulosin to help relax ureters to help pass stone, but does not seem to work well; IV fluids to flush out stone does not work; stones >5 mm need urologic intervention; many procedures, from retrograde uteroscopy to pull out stone to lithotripsy to break up stone to antegrade procedures to pull out stone; *recurrent stone former* — need to prevent future stones; increase water intake, make sure water intake sufficient to create 2.5 L of urine; specific recommendations depend on type of stone; *calcium oxalate stones* — reduce oxalate in diet (no blueberries, rhubarb, strawberries); low animal-fat diet can also help; do not restrict calcium; used to be advice, but decreased calcium allowed more oxalate to be absorbed, and patients had more stones; if urine calcium >300 mg in man and >250 mg in woman in 24 hrs, classified as hypercalciuria; use of thiazide-type diuretic can lower urine calcium and prevent future stones;, can supplement with potassium citrate; can use allopurinol in some patients, prevents nidus of stone and prevents development of stones; *calcium phosphate stones* — alkalotic urine drives stone development; many calcium phosphate stones result from drugs with carbonic anhydrase inhibitor effect, *eg*, topiramate, used for migraines, seizures, and weight loss; if patients taking this drug get calcium phosphate stones, may need to stop drug; focus on lowering pH; *uric acid stones* — result from very acidic urine; get urine pH >5.5 to prevent development; acidic urine caused by animal protein, chronic kidney disease, metabolic syndrome, and GI losses (diarrhea); first-line treatment, alkalinize urine, give patients potassium citrate or sodium bicarbonate; only type of stone in which therapy for preventing stones actually eliminates current stone; takes few wks to raise pH; *struvite stones* — result from infection with urease-producing bacteria; urease enzyme converts urea to ammonia and bicarbonate, unusual situation; usually ammonia only present in acidic urine, but because of local production of bicarbonate, have ammonia plus high pH, leading to precipitation of magnesium ammonium phosphate (aka struvite stone); requires chronic infection from urease-producing bacteria (*eg*, *Ureaplasma*, *Proteus*, staphylococcal species, *Klebsiella*, or *Pseudomonas* species), not from *E coli*; these stones more common in women; requires complete surgical removal of stone and followed by prolonged antibiotics; cannot treat with antibiotics alone (high rate of recurrence, can result in renal failure); if struvite stone, call urologist; need to completely clean out stones, very careful job, even if very small fragments remain, can be problematic; stones often asymptomatic; 1 case in which asymptomatic stone can be problematic; struvite stone can be seen on plain films; *Oxalobacter formigenes* — gut bacteria that consume oxalate; data show not everyone has *Oxalobacter formigenes*; people who have decreased urine oxalate and decreased risk of kidney stones have in gut; protects from kidney stones; taking antibiotics can wipe out *Oxalobacter* and increase risk for kidney stones in 6 to 9 mos

Suggested Reading

Cornelis T et al: The kidney in normal pregnancy and preeclampsia. *Semin Nephrol*. 2011;31(1):4-14; **Foxman B:** Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am*. 2014;28(1):1-13; **Frassetto L, Kohlstadt I:** Treatment and prevention of kidney stones: an update. *Am Fam Physician*. 2011;84(11):1234-42.

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Fluid, Electrolyte, and Acid-base Disorders

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Fluid and Volume Disorders

Body fluid: 2/3 of total body H_2O intracellular, 1/3 extracellular; within extracellular space, 3/4 interstitial and 1/4 intravascular; majority of fluid within intravascular space in venous capacitance vessels; arterial sensors (*ie*, baroreceptors) relate to circulatory fluid status, whereas chemoreceptors in hypothalamus relate to tonicity or osmolality

Hypovolemia: commonly referred to as dehydration (lack of H_2O); deficit of total body sodium (Na^+) as well as H_2O; those at risk include immobilized or bed-bound patients or those who have fevers, gastrointestinal (GI) illness (*eg*, vomiting, diarrhea), and individuals participating in high-exertion activities with heavy sweating thus at risk of insensible fluid loss; diagnosis includes history that suggests fluid loss or inability to replete fluid; physical exam includes low blood pressure (BP), orthostatic BP changes, low jugular venous pressure, dry mucous membranes, skin tenting, and poor or slow capillary refill; common laboratory data include elevated Na^+ concentration, elevated serum bicarbonate (HCO_3^-) suggesting metabolic or contraction alkalosis, and increased blood urea nitrogen (BUN)/creatinine ratio; treatment repletion with isotonic fluid, either intravenously (IV) with normal saline or balanced crystalloid solution or with oral rehydration therapy

Hypervolemia: volume overload reflecting an excess in total body Na^+ and H_2O, generally manifested as expansion of extracellular fluid volume in vascular or interstitial space, but not in circulating fluid; renal insufficiency patients with oliguria or anuria at risk; common causes include cirrhosis, nephrosis (nephrotic syndrome), and congestive heart failure (CHF); typically, diagnosis relies on history and physical; *physical exam findings* — may reflect increased BP, but may also reflect decreased if fluid overload accumulated in interstitial space but not effectively circulating; discordance between total body fluid and effective circulating fluid status; findings may suggest underlying disorder (*eg*, elevated jugular venous [JV] pressure may suggest CHF; basilar crackles and hypoxemia may suggest pulmonary edema related to left ventricular dysfunction; ascites and lower-extremity edema may be seen in patients with cirrhosis, CHF, or nephrotic syndrome); *common laboratory abnormalities* — hyponatremia, elevated brain natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (proBNP) levels in patients with CHF, hypoalbuminemia and liver-function test abnormalities in patients with liver disease; diagnosis of nephrotic syndrome requires elevation in urinary protein; *management* — limiting Na^+ and fluid intake; diuretics to help mobilize extra fluid; fluid removal may require inotropes or pressors as in patients with CHF with severe systolic dysfunction; dobutamine or dopamine with or without vasopressor may assist in diuretic therapy; in cirrhotic patients with vasodilatory physiology from portal hypertension, midodrine commonly used for vasoconstriction and to help effective circulating volume, so renal perfusion can be improved; dialytic therapies may be considered based on degree of renal function

Case 1: 45-year-old man with history of alcohol abuse presents to emergency department (ED) with altered level of consciousness; BP 85/50 mm Hg, heart rate (HR) 110 bpm, jaundice, notable ascites, scrotal and lower-extremity edema, overall disorientation; can say total body volume status elevated (hypervolemic) based on ascites, scrotal and lower extremity edema; based on BP 85/50 mm Hg, might suspect low effective circulating volume, discordant with overall volume status, reflecting increase in total body Na^+ and H_2O

Electrolyte Disorders

Disorders of osmolality (hyper- and hyponatremia): H_2O moves freely across cell membranes; Na^+ and potassium (K^+) most important electrolytes determining osmolality of extracellular and intracellular space, respectively; relationship maintained by ubiquitous Na^+/K^+ ATPase, pumping Na^+ out of cell and K^+ into it; serum Na^+ most important contributor to serum osmolality; blood urea nitrogen (BUN) and glucose also important, especially when elevated; serum osmolality $2*Na^+ + BUN/2.8 + glucose/18$; Na^+ is multiplied by 2 to account for accompanying anions such as chloride (Cl^-), and BUN and glucose divided by 2.8 and 18, respectively, to convert mg/dL to mmol/L as osmotic unit; some cells (*eg*, astrocytes in brain) sensitive to changes in osmolality, developed mechanisms to adapt to extracellular osmolality changes; important because adult brain encased in closed cranial cavity and osmolality changes (*eg*, shift towards hyponatremia) can cause swelling of these cells with no place for brain to expand; risk of cerebral edema would be herniation; in contrast, brain cells that rapidly shrink as result of quickly increasing extracellular osmolality causing H_2O to leave brain cells; can lead to osmotic demyelination if it happens too quickly for brain cells to adapt; process of adapting to osmolality changes by cells takes ~2 days

Hyponatremia: common electrolyte abnormality reflected by serum Na^+ concentration <135 mEq/L;

Na^+ concentration changes usually reflect too much H_2O relative to Na^+ rather than not enough Na^+; *typical workup* — check plasma osmolality, urine osmolality, urine Na^+, and assess patient's volume status; important to rule out other possibilities such as hyperglycemia or mannitol infusion, which can cause H_2O translocation from intracellular to extracellular space, thus diluting serum Na^+; common formula for hyperglycemia correction in hyponatremia, for each 100 mg/dL of glucose >100 mg/dL, Na^+ concentration drops by 1 mEq/L; in that scenario, plasma osmolality high despite hyponatremia; if plasma osmolality measures normal despite hyponatremia, 1 consideration pseudohyponatremia, where large macromolecules (*eg*, proteins, lipids) take up more space than electrolytes such as Na^+, thus diluting Na^+ by volume, though Na^+ concentration not truly low; may occur with high protein levels (*eg*, multiple myeloma) or high lipid levels (*eg*, severe hypertriglyceridemia); *most common scenario in hyponatremia* — plasma osmolality actually low, reflecting hypoosmotic hyponatremia; here, helpful to determine whether urine osmolality <100 mOsm/kg or >100 mOsm/kg; in severe hyponatremia, urine osmolality <100 mOsm/kg reflects very dilute urine as may be seen in patient with low solute intake (*eg*, tea-and-toast diet, beer potomania) and in psychogenic polydipsia; in both cases, patient's H_2O intake overwhelms kidney's ability to get rid of free H_2O; these patients commonly euvolemic; *treatment of patients with low solute intake and polydipsia* — increase solute intake, specifically Na^+ (as long as BP normal) and protein (composed of amino acids and components that ultimately generate urea, which will be used in free H_2O clearance by kidney); K^+ supplementation appropriate if patient has normal renal function and not at risk of hyperkalemia; *antidiuretic hormone (ADH; arginine vasopressin)* — elevation of urine osmolality significantly >100 mOsm/kg suggests high– ADH state; whether appropriate or not depends on clinical and physiologic state; appropriate ADH release should be expected in cases of hypovolemia (*eg*, vomiting, diarrhea), in which urine Na^+ concentration commonly low (*ie*, <20 mEq/L); high-ADH state seen in patients on diuretics who have been overdiuresed, especially with thiazide-type diuretics or in patients with decreased mineralocorticoid activity or hypoaldosteronism; ADH release may be somewhat appropriate in cases of hypervolemia with low effective circulating volume (*eg*, in cirrhosis, nephrosis, and CHF); in those cases, patients not taking diuretics commonly have low BP, low effective circulating volume, and would be Na^+ avid, reflected by low urine Na^+ concentration of (<20 mEq/L); elevated ADH state with edema and volume expansion normal in pregnancy; *treatment of hyponatremia* — determined by cause and volume status; clearly hypovolemic patients should be treated with repletion of volume with isotonic fluid, restriction of free H_2O; oral rehydration therapy good option for patients who can tolerate oral intake; management of hyponatremia in hypervolemic patients can be more complicated; as with hyponatremia, free H_2O should be restricted, but since hypervolemic patients have increased total body Na^+, usually prudent to avoid additional Na^+ intake and to help remove additional volume with diuretics, specifically loop diuretics; inotropic support or dialytic therapy may be needed depending on patient's BP and cardiovascular reserve

Syndrome of inappropriate ADH (SIADH): urine osmolality >100 mOsm/kg, reflecting high-ADH state; patients commonly euvolemic and urine Na^+ may be >20 mEq/L; causes and risk factors — nausea, vomiting, pain, disease of central nervous system or pulmonary system, and medications (*eg*, antidepressants, ecstasy as in illicit drug use); other common causes include hypothyroidism and glucocorticoid deficiency; *treatment* — restriction of free H_2O, correction of any thyroid or cortisol deficiencies, reviewing medications that may have caused SIADH, and controlling pain or nausea and vomiting; patients may be given salt tablets or hypertonic saline supplemented by loop diuretics; historically, demeclocycline (*eg*, Bioterciclin) has been used to treat hyponatremia related to SIADH, but vasopressin antagonists (vaptans) more commonly used recently; these medications expensive, run risk of overly rapid correction of hyponatremia, and warrant consultation with nephrologist; *rate of correction of hyponatremia* — determined by acuity in which hyponatremia developed, as well as symptoms and severity; because most patients develop hyponatremia over chronic or subacute period of >2 days to 3 days, rate of correction generally involves raising serum Na^+ concentration by 6 mEq/L or 8 mEq/L over 24 hrs and correcting by ≤16 mEq/L over 48 hrs; *overly rapid correction of hyponatremia* — risk of rapid cell shrinkage, resulting in osmotic demyelination and osmotic pontine myelitis; acute or severe hyponatremia concern about impending brain herniation; administer hypertonic saline to correct serum Na^+ concentration by 1 mEq/h to 2 mEq/h over 6 hrs (*ie*, increase in serum Na^+ concentration of 4-6 mEq/L over course of 6 hrs) and holding at that level for subsequent day; frequent lab checks important to confirm treatment strategy working but not correcting too quickly; helpful to follow urine osmolality to estimate how much free H_2O being cleared by kidney and will be left in serum on subsequent lab checks, and can help predict next serum Na^+ concentration; overly rapid correction of hyponatremia may also warrant DDAVP to keep Na^+ from rising too quickly; best done with nephrology consultation

Hypernatremia: Na^+ concentration of >145 mEq/L; volume depletion most common risk factor; dehydration and volume depletion can result from fluid loss from kidney or GI tract, insensible losses; in patients who have vomiting or diarrheal illness, bed-bound patients with no access to H_2O, elderly patients with abnormal thirst mechanism or ventilated patients with high insensible losses from pulmonary tract; different class of patients prone to hypernatremia have inappropriate ADH effect causing increased free H_2O loss and very dilute urine despite very concentrated plasma; ADH produced in hypothalamus and transported to posterior pituitary and released in response to high blood osmolality; extreme hypovolemia can also lead to ADH release; *issues leading to lack of ADH release* — neurosurgical procedures involving pituitary or pituitary stalk, malignancy with metastasis to hypothalamus or pituitary, autoimmune syndromes that affect pituitary or hypothalamus, and medications (*eg*,

lithium [*eg*, Eskalith]) that can decrease ADH effect in kidney, leading to very dilute urine and loss of free H_2O, culminating in hypernatremia; *management of hypernatremia* — involves H_2O-deficit calculation (basically % change of Na^+ from 140* total body H_2O), and usually effort to correct that hypernatremia over course of 2 days to 3 days, recognizing that overly rapid correction of hypernatremia could cause cellular swelling, brain edema, and risk of herniation

Original case: 45-year-old man with history of alcohol abuse who presented to ED with altered consciousness, 85/50 BP, HR 110 bpm; disoriented; jaundice, ascites, scrotal and lower-extremity edema; *laboratory data* — reported Na^+ 115 mEq/L, K^+ 3.2 mEq/L, Cl^- 90 mEq/L, HCO_3^- 20 mEq/L, BUN 18 mg/dL, creatinine 1.2 mg/dL, and glucose 100 mg/dL; plasma osmolality 245 mOsm/kg, notably below normal serum osmolality of ~290 mOsm/kg; with normal BUN and glucose levels, only hyponatremia noted on laboratory panel; no significant osmolar gap, confirmation of hypoosmolar hyponatremia; as other information provided, can consider differential diagnosis; in this patient with serum Na^+ 115 mEq/L, low plasma osmolality 245 mOsm/kg, urine osmolality returns at 250 mEq/L, and urine Na^+ concentration 15 mEq/L; already determined overall elevated volume status based on ascites and peripheral edema; *diagnosis* — based on low BP, determined low effective circulating volume status, likely important driving force of ADH (vasopressin) release; overall, differential diagnosis in person with elevated urine osmolality well above 100 mEq/L (250 mEq/L in this case), can determine ADH level very high; clinical determination to think whether high ADH level appropriate or inappropriate, because recognized low effective circulating volume, then would not say inappropriate ADH; low-solute diet (*eg*, beer potomania) may be considered with history of alcohol abuse, but can be ruled out because urine osmolality is well >100 mEq/L; hyponatremia may be attributed to hypervolemic clinical status and other stigmata that suggest liver cirrhosis and portal hypertension; low urine Na^+ concentration of 15 mEq/L (<20 mEq/L) also supportive, suggesting low effective circulating volume and Na^+-avid state; *management* — free H_2O restriction; Na^+ restriction may be suggested to prevent worsening ascites and volume overload; depending on BP and cardiovascular reserve, volume status may be corrected with paracentesis or diuresis; midodrine (Orvaten, Proamatine) or pressors may be required if hypertensive; other complicating factors (*eg*, hepatic encephalopathy, spontaneous bacterial peritonitis) may be considered; important in management of hypo- or hypernatremia to have frequent lab data drawn to confirm rate of correction not too fast

Potassium disorders: tight range (3.5 mEq/L to 5.0 mEq/L) of extracellular K^+ concentration; total body K^+ stores though very high, within cells; only ~2% of total body K^+ in extracellular fluid; concentration important for neurologic and muscular function; patients with K^+ disorders at risk of arrhythmias, muscle weakness, paralysis, or rhabdomyolysis

Hyperkalemia: K^+ concentration >5 mEq/L; K^+ shifts from intracellular to extracellular space; *common causes* — acidemia; lack of insulin (which helps activate) Na^+/K^+ ATPase; blockade of catecholamine receptors, and digoxin (Digitek, Digox, Lanoxin; inhibiting factor in Na^+/K^+ ATPase); conditions involving cell lysis (*eg*, rhabdomyolysis, tumor lysis syndrome, ischemic bowel, hemolysis); transfused cells or resorption of established hematoma; inability to clear K+ from body as in persons with abnormal kidney function, especially those with decreased urine output from CHF, low BP for other reasons, blockade of renin-angiotensin-aldosterone system, or anything that blocks aldosterone function at tubular level; *evaluation for hyperkalemia* — chemistry panel; electrocardiogram (ECG) to assess for peaked T-waves, prolonged PR interval, widening QRS (may culminate in ventricular fibrillation or ventricular tachycardia); *management of hyperkalemia* — determined by acuity and severity of abnormality; patients with cardiac arrhythmias require immediate stabilization of cardiac membranes with IV calcium gluconate or calcium chloride; insulin administration with glucose transiently shifts K^+ into cells; in severe acidemia, HCO_3^- can be given; all given in conjunction with review of medications that add extracellular K^+; beta agonists (*eg*, albuterol [ProAir, Proventil, Ventolin]) transiently shift K^+ into cells and mitigate effects of cardiac arrhythmia; diuretics remove K^+ and decrease total body K^+ level; sodium polystyrene sulfonate (Kalexate, Kayexalate, Kionex) or patiromer (Veltassa), which bind K^+ in GI tract, can be given, but use caution to avoid bowel necrosis with sodium polystyrene sulfonate (warrants use of bowel regimen or motility agent); patients not making urine or clinically unstable may require dialytic therapy and consultation from nephrologist, should be considered early with oliguric or anuric patients

Case 2: 63-year-old woman with history of hypertension and diabetes admitted for knee replacement; hospitalized for few days and developed postoperative urinary tract infection (UTI); routine morning labs showed new hyperkalemia; chemistry profile shows Na^+ 138 mEq/L, K^+ 5.6 mEq/L, Cl^- 110 mEq/L, HCO_3^- 22 mEq/L, BUN 24 mg/dL, creatinine 1.3 mg/dL, and glucose 115 mg/dL; medications that potentially contributed to her current hyperkalemia include lisinopril (blocks) angiotensin activity, subcutaneous heparin (can decrease aldosterone effect in distal tubule), trimethoprim component of trimethoprim/sulfamethoxazole (Bactrim, Septra, Sulfatrim) used for UTI by decreasing aldosterone activity, ibuprofen (*eg*, Advil) and other nonsteroidal anti-inflammatory drugs as well as COX-2 inhibitors, in conjunction with lisinopril (Prinivil , Qbrelis, Zestril), and ketoconazole (*eg*, Nizoral); not insulin

Hypokalemia: K^+ concentration <3.5 mEq/L; rate of change of K^+ as important as degree of K^+ abnormality; decreased K^+ concentration can be result of transcellular shift as well as total body loss of K^+; *common reasons for hypokalemia from transcellular shift* — alkalemia, treatment of hyperglycemia with insulin or sympathomimetic medications (*eg*, albuterol), which activate Na^+/K^+ ATPase and cause K^+ to shift into cells; less common, rapid cell formation such as treatment of megaloblastic anemia with vitamin B_{12}; also seen in post–cardiac arrest cooling; also less common, cellular channelopathies (*eg*, thyrotoxicosis in some Asian

or Mexican men that can lead to rapid intracellular shift and hypokalemia) and hypokalemic periodic paralysis (genetic disorder that can cause debilitating hypokalemia); *kidney related* — total body loss of K^+ can happen within kidney from different mechanisms such as hyperaldosterone state or related disease process such as primary hyperaldosteronism, Liddle syndrome, apparent mineralocorticoid excess, Cushing syndrome, or licorice ingestion; these scenarios typically present with hypokalemia and hypertension; in contrast, hypokalemia with hypotension may be seen with excessive diuretic use, loop and thiazide diuretics, as well as hypovolemia and metabolic alkalosis; in patients with acidosis (as noted on chemistry or blood gas) with concurrent hypokalemia, renal tubular acidosis and diabetic ketoacidosis should be considered (both cause renal K^+ wasting); monitoring K^+ loss from urine specimens collected over 24 hrs may help determine if K^+ loss from kidney or GI tract; K^+ loss of <20 mEq/d suggests nonrenal cause, whereas >30 mEq/d of K^+ suggests renal cause of hypokalemia; in GI tract, K^+ loss occurs from lower GI tract as in diarrheal illness or villous adenoma; *evaluation and diagnosis of hypokalemia* — chemistry panel; ECG; in contrast to hyperkalemia, common findings include U-waves, prolonged QT interval, as well as ventricular ectopy (*eg*, premature ventricular contractions, ventricular tachycardia); *other clinical sequelae that should be monitored in patients with severe hypokalemia* — ileus, respiratory weakness, as well as rhabdomyolysis (from which creatine kinase level might be checked); *treatment of hypokalemia* — determined by acuity and severity and whether repletion should be given IV or orally; typically KCl 40 mEq can be given orally and 10 mEq or 20 mEq can be given IV subject to central line availability; of particular interest *magnesium (Mg^{2+}) deficiency as cause of hypokalemia* — because of tubular management of K^+ and Mg^{2+}, total body hypomagnesemia can preclude proper reabsorption of K^+; cardiac patients being aggressively diuresed and on telemetry, with risk of arrhythmia, have chemistry panels to follow both K^+ and Mg^{2+} levels to ensure both in normal range; *other important factors* — blood gas if pH significantly abnormal (since correction of alkalemia that contributed to hypokalemia can lead to overcorrection) and hypercalcemia if patient develops acidosis; monitor urine output and consider telemetry; correction of volume status in case of hypovolemia and high-aldosterone state; hypomagnesemia can be seen with diuretic use and other channelopathies (*eg*, Bartter syndrome or Gitelman syndrome, roughly equivalent of inactivated channels of loop and thiazide diuretics, respectively); hypomagnesemia also may occur with diarrheal illness and malabsorption as well as chronic malnutrition, as seen in alcoholics, and from chronic use of proton pump inhibitors; hypermagnesemia not very common unless patient has renal insufficiency; only exception perhaps in women treated for preeclampsia with high-magnesium infusions

Acid-base Disorders

Overview: in acidosis, excessive acid accumulates in body; acidemia=culmination of that process in which pH below normal; similarly, alkalosis and alkalemia processes and culmination of those processes; primary disturbance should be recognized in acid-base analysis followed by recognition of compensation and whether compensation appropriate or not; never overcompensation in acid-base disorders, but may be mixed disorders (*eg*, respiratory alkalosis or acidosis) and concurrent metabolic acidosis or alkalosis; *evaluation of acid-base status* — blood gas; chemistry panel; in metabolic acidosis, expect pH and serum HCO_3^- to be low (<7.4 mEq/L and <24 mEq/L, respectively); may or may not be compensation in respiratory system, with decreased PCO_2; when metabolic acidosis recognized on blood gas and chemistry panel, important to assess anion gap (Na^+–Cl^-–HCO_3^- level); very low albumin levels suggest lower-than-normal expected anion gap; *most common reasons* — lactic acidosis, ketoacidosis, uremia leading to organic acid accumulation, and some ingestions and intoxications leading to increased anion gap acidosis; determining delta-delta (difference in measured vs expected anion gap compared with difference in measured vs normal HCO_3^- level) in anion gap acidosis, will guide whether superimposed non-anion gap metabolic acidosis or concurrent metabolic alkalosis

Lactic acidosis: common in hospitalized patients; *type A lactic acidosis* — results from tissue hypoperfusion as seen in shock, sepsis, cardiogenic hemorrhagic shock, ischemic bowel; type B lactic acidosis results from decreased clearance of lactic acid as may be seen in liver disease; increased metabolic or mitochondrial lactic acid generation, might be seen in patients taking metformin (*eg*, Glucophage; especially those with renal insufficiency), linezolid (Zyvox), propofol (*eg*, Diprivan), certain antiretroviral drugs; also, malignant cells can cause increase in lactic acidosis; *D-lactic acidosis* — D reflects D isomer of lactic acid; seen in patients with short gut or who have had GI bypass surgery; D-lactic acid produced by bacterial or prokaryotic cells if bacterial overgrowth in gut; provider should have high suspicion in certain patients (test not standard, must be ordered specifically); *management of lactic acidosis* — correct perfusion, if possible; administer exogenous HCO_3^- in profound acidosis, such as with pH <7.20 or <7.10, especially if risk of hemodynamic collapse; in patients with type B lactic acidosis, discontinue metformin, linezolid, or propofol; in D-lactic acidosis, decrease dietary carbohydrate and administer antibiotic therapy for any evidence of bacterial overgrowth in gut

Ketoacidosis: ketones can be detected in serum or urine; causes of ketoacidosis — diabetic ketoacidosis most common cause, especially in patients with type 1 diabetes with insulin deficiency; other causes include alcohol use and starvation; clearly elevated BUN and creatinine suggesting renal insufficiency and uremia can support diagnosis of anion gap acidosis from accumulation of waste products including phosphates and sulfates (can increase anion gap and cause acidosis); insidious anion gap acidosis not explained by lactic acidosis, ketoacidosis, or uremia may result from ingestion or intoxication with substance (classic gap-gap patients, may have anion gap as well as osmolar gap), should be considered especially when diagnosis not clear, history unconfirmed or if clear suspicion or evidence of intoxication or ingestion; common intoxications to consider are ethanol, methanol,

propylene glycol (can be used as solvent for lorazepam [Ativan] infusions), or ethylene glycol (antifreeze); consultation with nephrologist appropriate (hemodialysis may be involved); *treatment of ketoacidosis* — fomepizole (Antizol) or ethanol may be used to decrease metabolism of toxic ingestion (some metabolites considered more toxic)

Hyperchloremic metabolic acidosis: metabolic acidosis with normal anion gap; low pH and HCO_3^- levels; if proper compensation, partial pressure of CO_2 (PCO_2) may be low as well on blood gas; non-anion gap acidosis can be seen concurrently with anion gap metabolic acidosis; but may be case in which patient has clear metabolic acidosis noted on blood gas but anion gap not elevated, especially when considering albumin for expected anion gap; *evaluation* — in evaluating patients with non-anion gap metabolic acidosis, consider urine anion gap measurement (Na^++K^+–Cl^- concentrations), may be clue to the kidneys' ability to dispose of excessive acid; fractional excretion of HCO_3^- helpful in some cases; patients with normal anion gap metabolic acidosis generally fall into one of few categories; *type 1* — distal renal tubular acidosis (RTA); commonly leads to severe acidosis and hypokalemia; causes include autoimmune processes (*eg*, Sjögren syndrome, rheumatoid arthritis) and amphotericin administration; *type 2* — proximal RTA; may be part of Fanconi syndrome; also causes hypokalemia; may be caused by multiple myeloma, amyloidosis, acetazolamide administration, or heavy metal exposure; *type 4* — usually mildest form of RTA; hypoaldosterone; typically hyperkalemic; *other causes* — HCO_3^- loss from GI tract, as in diarrheal illness; dilutional (iatrogenic) cause (*eg*, in patient with volume depletion treated with normal saline with culmination of hyperchloremic metabolic acidosis); *treatment* — exogenous HCO_3^- therapy; balanced or buffered crystalloid solution (*eg*, PlasmaLyte, Isolyte) or lactated Ringer's may be considered, rather than normal saline, for IV fluid; important to recognize whether or not respiratory compensation appropriate; Winter's formula commonly used for compensation; in simple disorders, last 2 digits of blood-gas pH should roughly match blood-gas PCO_2; other considerations include risk of concurrent hyperkalemia, possible risk in severe acidosis of decreased catecholamine effect (vasodilation and decreased inotropic effect), and consequential hyperventilation in metabolic acidosis that can lead to respiratory fatigue

Metabolic alkalosis: increased blood gas pH and serum HCO_3^-; increased PCO_2 if respiratory compensation appropriate; *causes of metabolic alkalosis* — from gain in alkaline or HCO_3^-, iatrogenic or patients taking sucrose and calcium carbonate tablets (Tums); milk-alkali syndrome; other causes include acid loss (*ie*, loss of hydrogen proton and loss of Cl^- anion with steady HCO_3^-, as seen in contraction alkalosis and hypovolemia); *evaluation* — best guided with good understanding of BP and volume status; urine Cl^- level also helpful; acid loss culminating in metabolic alkalosis can happen from kidney loss, as happens with diuretic use as well as with Bartter and Gitelman syndromes (genetic channelopathies equivalent to diuretic overdose); urine Cl^- level in such cases high (>20 mEq/L); acid loss also seen in patients with vomiting or nasogastric tube set to wall suction; urine Cl^- level in such cases often low (<15 or <20); aldosterone state also helpful in understanding metabolic alkalosis; patients with low effective circulating volume (*eg*, patients with CHF or cirrhosis) may have elevated aldosterone state and be Na^+ avid, ultimately leading to aggressive Na^+ reabsorption in distal tubule of kidney and exchange of Na^+ for K^+ as well as hydrogen ions that can lead to both hypokalemia and alkalemia; *aldosterone* — primary hyperaldosteronism seen with hypertension can be cause of hypokalemia and alkalemia; secondary hyperaldosteronism from renal artery stenosis and Liddle syndrome; *treatment of metabolic alkalosis* — typically involves stopping diuretics; treat volume-depleted state with normal saline, volume-overloaded patient with acetazolamide (Diamox); in CHF patient aggressively diuresed with concurrent COPD and hypoventilation with respiratory acidosis and chronic compensatory metabolic alkalosis, acetazolamide may help manage severe alkalemia and volume overload; if patient with chronic respiratory acidosis compensated with elevated HCO_3^- intubated and corrected with aggressive ventilation, patient may have significant metabolic alkalemia or alkalosis during posthypercapnic period; metabolic alkalosis patients at risk of hypokalemia, so monitor K^+ level during correction; other issues include hypoventilation and decreased effective calcium (*ie*, low ionized calcium leading to tetany, seizures, cardiac arrhythmias)

Respiratory acid-base disorders: *respiratory acidosis* — patients with ventilatory defect develop respiratory acidosis that shows up in blood gas as low pH and increased PCO_2; if kidneys functioning normally, compensation should lead to increase in serum HCO_3^- level; degree of compensation depends on acuity or chronicity of respiratory acidosis; *respiratory alkalosis* — caused by hyperventilation that shows up on blood gas as elevated pH and decreased PCO_2; and acuity or chronicity of hyperventilation and respiratory alkalosis will determine metabolic compensation of decreased serum HCO_3^- level to bring pH back toward 7.40 mEq/L

Summary of acid-base disorders: Winter's formula helpful, especially with estimation rule; never overcompensate whether respiratory or metabolic (if PCO_2 lower than expected in metabolic acidosis, may be concurrent respiratory alkalosis); mechanisms for compensation will abate when pH approaches normal; metabolic compensation takes time, whereas respiratory response rapid; metabolic acidosis and alkalosis can happen at same time, whereas respiratory alkalosis and acidosis cannot

Case 3: 63-year-old man transferred from skilled nursing facility with lethargy; history of hypertension and coronary artery disease, dementia and dysphasia; systolic BP in 70s and HR in 120s; lethargic and somewhat tachypnic but protecting his airway; no ascites or peripheral edema; lab data show Na^+ 135 mEq/L, K^+ 4.9 mEq/L, Cl^- 103 mEq/L, and HCO_3^- 12 mEq/L; blood-gas pH 7.25, PCO_2 26; elevated anion gap of 20 (Na^+–Cl^-–HCO_3^-), so has anion gap acidosis; to work that up, consider lactic acid level and ketone, and confirm no acute kidney injury with uremic acidosis; use Winter's formula to determine expected PCO_2

with HCO_3^- of 12; PCO_2 of 26 quite close, suggesting appropriate respiratory compensation for metabolic acidosis; last 2 digits of pH often very close to PCO_2, suggesting appropriate compensation

Suggested Reading

Kamel KS et al, eds: *Fluid, Electrolyte and Acid-Base Physiology: A Problem-Based Approach.* 5th ed. Philadelphia, PA: Elsevier; 2016; **Reddi AS.** *Fluid, Electrolyte and Acid-Base Disorders: Clinical Evaluation and Management.* 2nd ed. New York, NY: Springer Science+Business Media; 2018; **Seifter JL et al:** Extracellular acid-base balance and ion transport between body fluid compartments. *Physiology.* 2017;32(5):367-79; **Zietse R et al:** Fluid, electrolyte and acid-base disorders associated with antibiotic therapy. *Nat Rev Nephrol.* 2009; 5(4):193-202.

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Stroke and Cognitive Impairment

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Pathogenesis of stroke: stroke not homogeneous disease; classified as either ischemic or hemorrhagic; ischemic strokes constitute approximately 85% of all strokes; hemorrhagic strokes — combination of intracerebral and subarachnoid hemorrhage; intracerebral hemorrhage much more common than subarachnoid (subarachnoid ~1% of all strokes); each behaves quite differently — has implications on workup and management

Ischemic stroke subtypes: several classification schemes; most widely used is TOAST classification based on trial in early 1990s); more accurate or detailed classification schemes gaining traction; basic categories similar

- Large-artery atherosclerotic disease stroke: attributed to atherosclerotic plaque causing >50% stenosis of supra-aortic vessels; classic carotid stenosis leading to stroke — characteristic example of large-artery atherosclerotic stroke; large-artery atherosclerosis also encompasses intracranial stenosis, *eg*, significant stenosis of left or right middle cerebral artery; more common in Asian (30%-40%) vs Caucasian patients; aortic arch atheromas also belong to this category, although more difficult to classify
- Cardioembolic stroke: attributed to emboli that stem from the heart; atrial fibrillation (AFib) most common cause; other causes include left ventricular thrombi, depressed ejection fraction leading to hypokinesis and clot formation, vegetation on heart valves; clinically significant (<35%); patent foramen ovale PFO) also implicated
- Lacunar/small-vessel strokes: first described as clinical syndromes; caused by occlusions of small, penetrating terminal vessels that lie deep in brain; not cortical strokes; basal ganglia, thalamus, and pons most commonly affected; lacunar stroke refers to both imaging appearance and clinical syndrome; traditionally linked to cardiovascular risk factors, especially diabetes and hypertension (HTN); more common in southeastern areas of the United States — "stroke belt"
- Strokes of undetermined source: contested issue because many strokes are labeled as undetermined, but haven't had sufficient work-up; umbrella category; embolic stroke of unknown source (ESUS) — stroke that appears embolic; not as small as small-vessel stroke appears in imaging; looks like it arose from a clot, but cannot find cause; in 25% to 25% of patients, exact cause cannot be identified; no vessel stenosis, no structural heart abnormality, and no detectable AFib; important category because even if no cause is found, may be able to find treatment (anticoagulation); ongoing trials targeting ESUS patients with new oral anticoagulants
- Other rare causes: arterial dissections most common cause of stroke in young people; strokes caused by hypercoagulable conditions, *eg*, antiphospholipid syndrome, cancer-related hypercoagulability

Intracerebral hemorrhage (ICH): somewhat heterogeneous; main categories are deep (subcortical) and superficial (cortical or lobar) hemorrhage; topographic classification with etiologic implications; deep hemorrhages (*ie*, basal ganglia, thalami, internal capsule, pons) more likely to result from HTN; lobar hemorrhages more likely to result from cerebral amyloid angiopathy — caused by deposition of beta amyloid in vessel wall, leading to friability, rupture, and bleeding; seem to harbor specific alleles of the apoE lipoprotein

- Subarachnoid hemorrhage: contributes to small subset of hemorrhagic strokes; aneurysm rupture most common cause–usually quite massive; affects large cisterns in base of brain; also *convexal subarachnoid hemorrhage:* small hemorrhage in sulci on top of brain (hence, convexal); can pose significant diagnostic dilemma; usually no underlying vascular problem, no aneurysm; depending on age of patient, can be result of amyloid angiopathy (age >55 yrs) or reversible cerebral vasoconstriction (RCVS; age <55 yrs)

Prevalence and incidence: >750,000 new strokes per year in US; overall prevalence in US population about 3% to 4%; substantial variance in prevalence among different states (higher in stroke belt); *eg*, Alabama: >4%, Massachusetts: 1.8%

Acute management and workup of acute ischemic stroke: if stroke suspected, immediate referral to ED for further evaluation; starts with alerting EMS; most important: determine time patient last known to be well; in patients with unwitnessed time of symptom onset, clock set at time patient last seen normal (*eg*, if patient wakes up with plegia and aphasia at 6:00 or 7:00 AM and last seen well 10:00 PM previous night, that is when clock starts ticking); vital importance — influences subsequent actions; first, try to determine patient eligible for IV thrombolysis and/or mechanical thrombectomy to remove clot; next, perform acute clinical evaluation (done within 1-2 minutes); use National Institutes of Health Stroke Scale (NIHSS; 11-item scale that provides scoring or points in different domains: motor, language, speech, gaze, *etc*); stroke scale of 0 — normal; maximum 42 points; quick screening tool, well validated, can be done quickly at bedside; impossible to

know from clinical presentation whether patient suffered hemorrhagic or ischemic stroke

Ischemic vs hemorrhagic stroke: some features such as headache and progression of symptoms can be more subacute in hemorrhage as hematoma expands; cannot know whether patient with severe neurologic deficit has ischemic or hemorrhagic stroke; aspirin or any other antithrombotic medication should not be given acutely before imaging studies performed

Head imaging: *noncontrast computed tomography (CT):* exclude bleed, large tumor, or large evolving ischemic stroke — contraindication to give intravenous (IV) tissue plasminogen activator (tPA); per *American Heart Association (AHA) guidelines:* head CT within 10 mins from time when code stroke alerted; after last time known well, documented estimation of neurologic severity by NIHSS, and CT that shows no hemorrhage, think about IV tPA; well-known contraindications to IV tPA include recent major surgery or head trauma; consult institutional guidelines regarding contraindications

Labs: fingerstick; high or low blood glucose can mimic stroke; patient can have focal neurologic deficits from hypo- or hyperglycemia

IV thrombolysis: AHA published specific addendum addressing scientific rationale behind selection criteria; unless reason to suspect coagulopathy from medical condition (*eg*, hepatic dysfunction) or known/suspected exposure to anticoagulation medications, no reason to delay IV thrombolysis; at 0 to 3 hrs, every patient without contraindication eligible for IV tPA in US (standard of care and should be given) — per FDA label; in Europe, window for IV-tPA is 0 to 4.5 hrs; per AHA, possible to consider administering thrombolysis to patients within 3 to 4.5 hrs; patients with ≥2 criteria (aged >80 years, diabetes, prior stroke, or a severe stroke with NIHSS of >25) should not be given IV tPA; often discussion with patient and/or family members about pros and cons; individualized decision, so may end up giving IV tPA within 3 to 4.5 hrs

Thrombectomy: trials noted patients with documented large-vessel occlusion benefit if treated between 0 and 6 hrs; must have documented vessel occlusion; in addition to head CT, CT angiogram (CTA) of head and neck commonly performed — fast, sensitive, specific method that shows whether patient has large-vessel occlusion and eligible for thrombectomy; clinical severity may give indirect evidence of large-vessel occlusion; NIHSS ≥10 suggestive of large-vessel occlusion; in addition to IV thrombolysis, patients with large-vessel occlusion and no contraindications should also be offered IV thrombectomy; time window between 6 and 24 hrs: move from time limits to physiological substrates

Variability among patients in rate of progression from vessel occlusion to complete infarction — determined by collateral circulation; patients may have middle cerebral artery (MCA) occlusion and progress to full-blown MCA infarction within 1 hr; others resist ischemia for many hours; some patients may benefit beyond 6 hrs because they progress more slowly

Clinical trials: decisions based on the DAWN and DEFUSE trials, which employed advanced imaging (magnetic resonance imaging [MRI] or CT perfusion) and used automated software to automatically provide information about amount of core infarction and amount of tissue at risk; do CT perfusion and decide based on certain thresholds between tissue at risk and dead tissue, or clinical imaging dissociation; patients with substantial clinical deficit eligible for thrombectomy; in properly selected patients, thrombectomy works well, if done by experienced person, even after 24 hours; having received IV tPA not contraindication

Blood pressure (BP) control in acute phase: IV thrombolysis — special scenario — for first 24 hrs, do not want to exceed systolic of 185 and diastolic of 100; beyond that, IV-tPA patient treated same way as any other stroke patient; very low (<120) or high (>200) BP not good; in practice, use autoregulation, or permissive HTN; allows blood flow in hypoperfused areas of tissue bordering on ischemia; guideline states BP management in acute phase should be individualized; reasonable to resume or start antihypertensives in those who have HTN once stable; no specific time limit or BP target

Aspirin: in patient not eligible for IV tPA or thrombectomy, or in any patient with acute ischemic stroke, aspirin recommended within first 48 hours; patient given full-dose aspirin followed by 81 mg daily; dose then modified depending on underlying pathology and etiology; same goes for deep vein thrombosis (DVT) prophylaxis: important to start aspirin as soon as possible — DVT and other complications frequent after stroke

Blood glucose control: association between elevated blood glucose and poor outcome; physiology not well understood; hypoglycemia as bad as hyperglycemia; ongoing SHINE trial may address this issue; current guideline and practice allow for liberal blood sugar target (120-180 mg/dL) in acute phase; AHA and American Diabetes Association (ADA) guidelines differ regarding long-term dysglycemia management

Dysphagia screening: patients often suffer aspiration pneumonias; frequent cause of mortality and morbidity post ischemic stroke; recommended that patients undergo dysphagia screening as soon as possible; better outcomes when standardized, comprehensive dysphagia screening tool employed; performed at bedside; speech therapist can do more sophisticated studies

Acute management of hemorrhagic stroke: perform imaging studies; to determine diagnosis; 2 types — deep and lobar hemorrhage; no difference in clinical approach; hemorrhagic stroke often perceived as less acute, not addressed with same sense of urgency; can have catastrophic consequences if not dealt with as stroke; *major difference from ischemic stroke:* patients will not get thrombolysis but will get BP management

BP management: BP predisposing factor for hemorrhagic stroke and predicts worse outcome; goal of INTERACT and ATACH-II trials — to see whether lowering BP to <140 in acute phase safe and efficacious; shown to be safe, efficacy signal not strong; per AHA recommendations, reasonable and safe to achieve BP control in acute phase; institutional guidelines recommend acute lowering of BP to <140; how to achieve that relies on discretion of practicing clinicians and availability of medications; often, labetalol first treatment; patients, because of predisposition, longstanding untreated HTN, and because of adrenergic

surge in acute phase, have HTN that often necessitates continuous infusion; nicardipine go-to medication; recommend against using nitroprusside — causes vasodilation, which can result in increased intracranial pressure

Stroke scales: for acute assessment of ICH severity, NIHSS (as with ischemic stroke); other scales used as well — intracerebral (ICH) score (probably most well known), which takes into account Glasgow coma scale — level of alertness, size of bleed, presence of intraventricular extension, and location (brainstem or supratentorial); ICH score originally meant to be communication tool, not prognostication tool; however, often used as such

Surgical care: first STICH trial targeted all types of ICH; did not show benefit with surgical vs best medical care; however, signal that superficial hemorrhages (<1 cm from surface) might benefit; therefore, STICH II trial conducted — also did not show any benefit; several ongoing studies with minimally invasive tactics, including MISTIE trial; in MISTIE, microcatheter inserted stereotactically, tPA infused locally, then hematoma dissolved and suctioned out; very different from craniotomy; several studies have targeted intraventricular hemorrhage and used tPA to dissolve clot; early results encouraging, but most recent phase 3 study unsuccessful; subsequent study targeting patients with larger volumes of intraventricular blood; used in individual cases, but not standard of care; external ventricular drainage also used; individual treatment decisions depending on opinion of physicians involved

Coagulation factor supplementation: no room for routine use in ICH; however, subsets of patients have known coagulopathy and seem to benefit from correction of coagulopathy; most common scenario: patient who has bleed while on warfarin; was main population until recently with novel oral anticoagulants (NOACs); for many years, used fresh frozen plasma (FFP), which corrects coagulopathy, but causes extra volume for patient; 4-factor prothrombin concentrates correct coagulation much faster — no delay for thawing plasma as with FFP; also, volume used is much lower; recommended to use prothrombin complex concentrate instead of FFP — works somewhat later when used with vitamin K; target INR ≤1.4 in acute ICH; try to achieve as quickly as possible; metric used by the AHA to determine how well tertiary stroke center works in field of ICH; observational data show that quick correction seems to confer better outcome; new oral anticoagulants include dabigatran (Pradaxa) and factor Xa inhibitors; usual coagulation factors do not necessarily work; when these medications first came out, unclear what to do in patients who have bleed while on NOAC

Now have some antidotes (reversal agents): reversal agent for dabigatran, idarucizumab (Praxbind) — monoclonal antibody (mAb) that removes dabigatran within minutes and corrects thrombin time quickly; FDA approved and should be used; phase 4 observational data will show if it has anticipated efficacy; with regard to factor Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and, to lesser degree, edoxaban (Lixiana, Savaysa; not widely used in the US), and the reversal agent andexanet (Annexa); recently approved by the FDA but limited efficacy data

Follow-up imaging: follow-up CT scan within 12 to 24 hrs to establish stability — some patients have expansion of hematoma and worsen

Seizure precaution: unless patient has clear clinical or electrographic seizure activity, should not be given antiepileptics

DVT prophylaxis: current recommendation to start DVT prophylaxis within 24 to 48 hrs after establishing stability of hematoma with serial CT scans

Other management: basically same as for ischemic stroke (*eg*, blood glucose, dysphagia screening, rehabilitation); to date, no agent with proven efficacy

Outcomes: hemorrhagic stroke perceived as more severe than ischemic stroke; because of perceived poor outcomes of hemorrhagic stroke, patients not offered aggressive therapy — therefore, patients die and have worse prognosis than with ischemic stroke; however, patients may do the same as or better than, those with ischemic stroke; recovery may be slower; most potent prognosticative factors for poor outcome — physician perception and early termination of care; AHA recommends that patients offered full support for ≥48 hrs; depending on wishes and circumstances, clinicians can make decisions after talking to family and/or patient; subacute can result because of release of free radicals

Secondary prevention of stroke and transient ischemic attack (TIA): TIA no different from ischemic stroke in terms of preventive measures; for many years, TIA defined as neurologic deficit <24 hrs; anything more considered stroke; now define TIA and stroke with imaging criteria; often patient with resolution of clinical symptoms has MRI evidence showing small stroke; some literature suggests patients with MRI-positive TIAs have higher likelihood of subsequent stroke; now TIA taken as seriously as stroke

Laboratory workup: lipid panel with specific attention to LDL and glycosylated hemoglobin ($HgA1_c$); TSH used to be included in stroke workup, but has no real utility; often, patients with diabetes have stroke and vice versa; American Stroke Association (ASA) defers to ADA recommendations for long-term management; most dysglycemic states, impaired glucose tolerance and full-blown diabetes, confer high risk of stroke; patients should have good glycemic control; cholesterol somewhat more complex; low-density lipoprotein (LDL) goal <100, <70 in diabetic patient; patients differ when it comes to cholesterol management; American College of Cardiology (ACC) recommends stratifying patients according to other risk factors (*eg*, diabetes, HTN) when targeting cholesterol; look at whole patient before treating with lipid-lowering agents; certain stroke subtypes benefit more from addressing cholesterol; atherosclerosis more heavily dependent on hypercholesterolemia than other risk factors; patients who have large-artery atherosclerotic strokes more likely to benefit from statins; much benefit independent of lipid-lowering effect of statins, but related to pleiotropic effects of plaque stabilization; high-dose statins and strict LDL goals recommended for patients with carotid plaque or high-grade intracranial stenosis

Routine cardiac imaging: controversial issue; until 2013, AHA did not take direct stance; European stroke guideline suggests it should be done in select patients; in real-world situations, transthoracic echocardiogram (TTE) has been used almost as standard of care; in 2018, ASA guideline recommends against the routine use of TTE; will be evolving issue; in tertiary stroke center where with many complex cases, tend to want a TTE in most patients; in patient without cardiac history and documented large-vessel atherosclerotic stroke, utility and extra benefit from TTE will be low; in patient with suspected cardioembolic pathology, TTE will yield important information; bubble study done specifically to see if right-to-left shunt or PFO exists; does not make sense to do it in older patients in whom PFO less likely to be implicated in stroke pathogenesis even if present, and also in whom even if one is found, will not address it; probably more important to do in younger patients — also important to perform transesophageal echocardiogram (TEE) if everything else negative in terms of stroke workup because a TEE more sensitive than TTE in detecting PFO

Coagulation pathology checkup: in select patients with no other risk factors, in younger patients, or in patients with family or personal medical history (*eg*, a woman with many miscarriages), makes sense to check for antiphospholipid syndrome coagulopathy such as factor V Leiden or prothrombin gene mutation; genetic factors have low yield, and even if one finds something, often difficult to determine their role in stroke pathogenesis

Long-term heart monitoring: to detect atrial fibrillation; 24 to 48 hrs of continuous monitoring in hospital not enough; 30 days of monitoring better than 1 to 2 weeks; implantable loop recorders that check for up to 3 years better than routine checkup with EKG

Anticoagulation: all patients who have documented AFib should be on anticoagulation; use stratification score such as CHADS-VASc; until recently, only warfarin; now more options — dabigatran, apixaban, rivaroxaban, and edoxaban — which have significant advantages; no need for monitoring of blood tests, dietary restrictions, and much easier to take; noninferior to warfarin in all trials; patients prefer NOACs most of time, especially now that antidotes or reversal agents available, although cost often issue; strongly recommend checking with patient's insurance before prescribing — out-of-pocket costs can be obstacle; NOACs seem safer than warfarin; lower bleeding rates, except for dabigatran, which seems to have higher GI bleeding; intracranial hemorrhage lower with all 3 agents

Endarterectomy: with reasonably high-grade asymptomatic carotid stenosis (≥70%), patient should be operated on as quickly as possible; no evidence to support strategy of delaying endarterectomy until patient stable; benefit of endarterectomy diminishes with time from index stroke; consider comorbidities, patient wishes, and surgical expertise; reasonable to pursue endarterectomy in big center with experienced surgeons; complication rates usually low; asymptomatic carotid disease more problematic; relevant trials showed long-term benefit with surgery vs medical management with high-grade stenosis; having asymptomatic high-grade carotid stenosis does not equal intervention; need to discuss with interventionalists and make sure patient medically optimized before proceeding to intervention; recommend patients achieve normotension; no specific antihypertensive agent for stroke prevention; if patient has good reason to be on statin, having bleed, no reason to hold it; if patient has reasonably low LDL, no compelling reason to be on statin, and has bleed in brain, probably makes sense to hold it and monitor LDL

Antithrombotic use: unless the patient has specific need or reason to be on anticoagulant, usually use antithrombotic antiplatelet medication; CAPRIE study showed some benefit of clopidogrel (Plavix) vs aspirin, but study driven mostly by peripheral arterial disease; AHA has no specific recommendation on choice of agent — discretion of the clinician and other patient needs; for patient with cardiac stent who needs to be on antiplatelet therapy, clopidogrel necessary; long-term dual antiplatelet therapy has no role in stroke prevention; seems to be preventive benefit early on, outbalanced by increased bleeding risk; Chinese study showed patients benefit from being on dual antiplatelet vs aspirin alone for 3 months; in mid-May 2018, large study replicated those results in American and European patient population; from these data, good strategy would be to use aspirin and clopidogrel for 30 days and then resort to single antiplatelet; additional benefits in patients with known large-vessel atherosclerosis, intracranial stenosis, or carotid stenosis

PFO: 25% to 30% of the population has PFO; finding PFO does not mean that it has anything to do with stroke; we use risk-stratification schemes to make sure patient has no other explanation for stroke; until recently, PFO closure did not seem to confer any benefit over medical management; more recent studies included patients with well-documented lack of other explanation (*ie*, truly cryptogenic strokes); patients with PFOs who had high-risk characteristics; seems to be some benefit in long-term prevention; data suggest closure in select patients might be reasonable; very important that patient has been given very thorough workup to exclude any other possible cause before discussing PFO closure; necessary to refer to cardiologist with this experience necessary

Intracranial aneurysms and subarachnoid hemorrhage: aneurysms develop mostly during life — not congenital; in US, prevalence of unruptured aneurysms estimated at ~2.5%, and proportion increases with age; risk factors include HTN, smoking, and excessive alcohol intake, all of which nearly double risk; only about 20% of patients with ruptured aneurysm have some strenuous physical activity preceding it; nonmodifiable risk factors include increasing age, female sex, Finnish or Japanese ethnicity (could be due to reporting or detection bias), history of prior subarachnoid, and aneurysm characteristics (*eg*, size, location, shape); risk factors for aneurysm and rupture seem to converge — so common factors for both having unruptured aneurysm and rupture of aneurysm; some genetic disorders predispose to aneurysms, including adult polycystic kidney disease (up to 10 times or higher risk), Ehlers–Danlos type 4, and bicuspid aortic valve; genetic disorders account for <10% of subarachnoid; modifiable risk factors account for nearly two-thirds of risk; common sites for unruptured aneurysms — bifurcations of intracranial vessels — anterior communicating artery, posterior communicating artery, bifurcation of MCA, top of the basilar artery;

most discovered during workup for another ruptured aneurysm; second most common reason — headache, about 25%; some have transient neurologic symptoms and suspected TIA or stroke, which leads to workup

Natural history: most of this information comes from 1 seminal study — international study of unruptured intracranial aneurysms (ISUIA); retrospective aspect, found that aneurysms >10 mm have 20-fold higher risk of rupture; absolute risk not that high; subsequent part of study revealed new "magic" number — 7 mm in terms of size; also showed that location dangerous — posterior circulation aneurysms more likely to rupture; combination of size and location taken into account; bigger aneurysms more likely to rupture, but most ruptured aneurysms small

Treatment decisions: experienced neurosurgeon with expertise in vascular neurosurgery is best person to address these issues; PHASES score (risk-stratification tool) uses risk factors and plots them to give risk of rupture

Screening and monitoring: ASA recommends patients with >2 family members with intracranial aneurysm or subarachnoid should be offered aneurysmal screening by CTA or MRA; patients with history of autosomal dominant polycystic kidney disease, especially those with family history of intracranial aneurysm, should be offered screening; optimal interval and duration of follow-up in someone with unruptured aneurysm — uncertain; for patients managed noninvasively who have no contraindication, makes sense to consider time-of-flight MRA as a long-term follow-up; although CT angiograms better in detecting aneurysms, they have radiation and contrast exposure as opposed to time-of-flight MRA, which just looks at blood flow; new techniques emerging

Clinical presentation of subarachnoid: most well-known presenting symptom: "thunderclap headache," described as "worst headache of life"; pose question to patient as something like, "Tell me, how quickly did your headache go from onset to maximum intensity? Was it seconds, minutes, or hours?"; other findings, *eg*, nausea, vomiting, meningismus, photophobia, depressed level of consciousness, and focal neurologic deficits, differentiate subarachnoid hemorrhage from both ischemic and hemorrhagic ICH; some patients suffer "sentinel blood leak" — good predictor of subsequent rupture, but difficult to know whether patient with headache has sentinel leak and if should be worked up for aneurysm; headache probably most common presenting symptom in ER, but only 1% of headache due to atraumatic subarachnoid hemorrhage; taking into account patient family history, if the patient describes thunderclap headache, increases level of suspicion to look for sentinel leak

Clinical severity scales: different from the NIHSS or the ICH score; the Hunt and Hess scale most important and well known; takes into account level of consciousness and presence/absence of focal neurologic deficits; another scale — World Federation of Neurological Surgeons Grading System; firm recommendation that initial clinical severity of atraumatic subarachnoid determined by use of simple validated scales

Imaging work-up: noncontrast head CT — most important first step; well-contrasted head CT has good sensitivity and specificity of detecting subarachnoid hemorrhage; sensitivity decreases sharply after 5 to 7 days because blood absorbed; negative head CT should not negate subarachnoid; gold standard — digital subsection angiography or conventional angiography; should be used in any patient with suspected aneurysm; CTA has good sensitivity and specificity; reasonable alternative to conventional angiogram, although more likely to miss aneurysm ≤3 mm; MRA also decent but not good specificity for small aneurysms

Lumbar puncture — important complement to head CT — should always be considered in patient with symptoms suggestive of ruptured aneurysm but no subarachnoid on head CT; allow ≥6 to 12 hrs from symptom onset to avoid false negatives; if tap done quickly and blood has not started to degrade, will only see red blood cells; cannot distinguish between atraumatic tap and subarachnoid blood; if doing tap in suspected subarachnoid hemorrhage, always ask lab for spinning xanthochromia

Suggested Reading

Connolly ES Jr et al: Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43(6):1711-37; **Hemphill JC 3rd et al:** Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(7):2032-60; **Kernan WN et al:** Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-236; **Powers WJ et al:** 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(3):e46-110.

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Obesity and Metabolic Syndrome

Caroline Apovian, MD, *Professor of Medicine and Pediatrics, Boston University School of Medicine; Director, Center for Nutrition and Weight Management, Boston Medical Center, Boston, MA*

International overview: the US leads the world in prevalence of overweight and obesity; steady increase in obesity rates from about 1970, with no end in sight; steady increase in obesity rates predicted until at least 2030; in 2030, obesity levels expected to be particularly high in the US, Mexico, and England — 47%, 39%, and 35% of the population, respectively, projected to have obesity; increase suspected to be weaker in other areas of the world such as Italy and Korea, with projected obesity rates of 13% and 9%, respectively; incidence of obesity in France projected to nearly match that of Spain, at 21%; obesity projected to increase more rapidly in Korea and Switzerland, where, historically, rates have been low; currently ~99 million patients with obesity in the US and 15 million in the UK

Definitions: *obesity* — excess adipose tissue; hard to measure on a population level, so body mass index (BMI) is used; *BMI* — weight in kg divided by height in m^2

Categories: BMI <18.5 — underweight; BMI 18.5-24.9 — normal weight; BMI >25 — overweight; BMI >30 — obesity; *obesity divided into classes* — BMI 30-35 — class 1 obesity; BMI 35-40 — class 2 obesity; BMI >40 — class 3 obesity

Concern for US: overweight and obesity is public health crisis in the US

US data: 31% of population either normal weight or underweight; 69% of American adults overweight or have obesity; 34% overweight; 35.1% obesity; 20.6% obesity class 1; 8.1% class 2; 6.4% class 3; 99 million people with overweight or obesity in US (15 million in UK)

Medical costs: direct medical costs of $147 billion/yr in 2009 in the US (>9% of all medical spending); current costs probably higher; people with obesity spend almost $1500/yr more on health care — ~41% more than persons of average weight; associated disability and early deaths add to toll

Obesity and Disease

Overview: pathology becoming clearer; chronic state of inflammation caused by excess fat tissue; fat tissue deemed to be endocrine organ, secreting proteins and adipokines that enter other organ systems and cause dysfunction; excess production of some adipose tissue hormones, suppression of others; in combination with recruitment of immune tissue and inflammatory cells, appears to produce many illnesses associated with obesity; explains how such conditions as arthritis, diabetes, heart disease, and cancer can be more frequent in patients with obesity

Associated changes: elevated levels of free fatty acids from fat tissue cause increase in hyperinsulinemia and insulin resistance as well as dyslipidemia; increase in other hormones, such as angiotensinogen, causes hypertension; increase in plasminogen activator inhibitor-1 (PAI-1) associated with thrombosis; also elevated estrogen levels; adipokines (*eg*, TNFα and IL-6) can cause inflammation, leading to osteoarthritis, other types of arthritis, and certain cancers; decrease in beneficial hormones such as adiponectin can cause insulin resistance and type 2 diabetes; other factors secreted by adipose tissue include adipsin, fatty acids, resistin, retinol, and tumor necrosis factor alpha (TNFα); also high-sensitivity C-reactive protein (hsCRP), which can be measured in blood and can be considered a surrogate for increased inflammation; interleukins (*eg*, IL-6, IL-8) and TNFα

Location of ectopic fat: *ectopic fat* — excess adipose tissue stored in body; risk for other disorders depends on location of ectopic fat stored in body; deposits associated with metabolic disorders; *visceral fat* — ectopic fat stored in viscera; can be assessed by measuring waist circumference; association between visceral fat and insulin resistance; increase in visceral fat causes more inflammation, macrophage infiltration, insulin resistance, altered release of adipokines, free fatty acid metabolites, and oxidative stress than subcutaneous fat in other areas (*eg*, gluteal area, hips); pancreatic fat associated with beta-cell dysfunction and insulin resistance; ectopic fat around heart and kidneys can also cause inflammation and dysfunction in those organs

Metabolic Syndrome

Diagnosis: measure waist circumference (signaling central adiposity) — waist circumference >40" in men, >35" in women; increased inflammatory factors (*eg*, free fatty acids, PAI-1, IL-6, TNFα, angiotensinogen); decrease in adiponectin; vital signs; hypertension; elevated fasting blood glucose (FBG) and hemoglobin $A1_c$; dyslipidemia with increased large very-low-density lipoprotein (VLDL), increased small low-density lipoprotein (LDL), and decreased large high-density lipoprotein (HDL); elevated triglycerides

Other characteristics: predisposition to developing type 2 diabetes from insulin resistance (higher level of visceral body fat = higher risk for insulin resistance); *prediabetes* — elevated FBG and hemoglobin $A1_c$; dysfunctional endothelium with inflammation, dysfibrinolysis, vascular reactivity, and foam-cell proliferation

Associated Conditions

Comorbidities linked to obesity: increased from 21 to >200 conditions — type 2 diabetes, coronary artery disease, pulmonary embolism, myocardial infarction, stress incontinence, ischemic stroke, heart failure, chronic kidney disease, gallbladder disease, sleep apnea, asthma, depression, chronic obstructive pulmonary disease (COPD), hypoventilation syndrome, osteoarthritis, hypertension, gastroesophageal reflux disease (GERD), nonalcoholic fatty liver disease; metabolic syndrome

Most prevalent and expensive annually: osteoarthritis, hypertensive diseases, dyslipidemia; GERD (also associated with significant medication expenses); chronic low back pain

Obesity as a Disease

Recognition as a disease: obesity designated as disease by American Medical Association (AMA) in 2013; many other organizations have endorsed this designation; should be treated as chronic disease

Secondary causes: hypothalamic obesity (usually diagnosed in childhood); hypothyroidism can exacerbate obesity but usually does not cause it

Other considerations: polycystic ovarian syndrome (PCOS) can exacerbate obesity and often lead to type 2 diabetes

Diagnosis and Management

Overview: in 2013, American Heart Association (AHA), American College of Cardiology (ACC), and Obesity Society developed and published guidelines for management of overweight and obesity in adults; published in *Journal of American College of Cardiology*, *Circulation*, and *Obesity*; intended as guidelines for primary care providers (PCPs) and other health care providers (HCPs) to treat overweight and obesity with diet, exercise, and to refer patients for surgery

2013 obesity guidelines: use BMI and waist circumference to identify patients at risk; advise patients of their risks and how risks are increased; evidence in literature shows that 3% to 5% sustained weight loss reduces risk factors as well as risk of type 2 diabetes in patients with overweight or obesity and who can lose that amount of weight; *strong recommendation* — advise patients with obesity who meet criteria for surgery that bariatric surgery may be option; prescribe face-to-face or telephone-delivered weight-loss maintenance programs that provide regular contact (at least monthly) with trained interventionist to engage them in high levels of physical activity, to monitor body weight regularly, and to consume reduced-calorie diet; higher level of physical activity = 200 to 300 minutes/wk

Diets: highlights from 2013 obesity guidelines state there is really no ideal diet; based on studies and meta-analyses of diets for weight loss; not true that Weight Watchers diet is best for weight loss: Weight Watchers is program, not diet; uses low-fat approaches and calories to reduce body weight

Diet recommendations: PCP should prescribe set number of calories per day based on individual needs; usually subtract 500 or 1000 calories a day; advise patients to choose diet they can adhere to; prescribe diet to achieve reduced calorie intake for individuals who would benefit from weight loss as part of comprehensive lifestyle intervention — 1200 to 1500 calories/day for women, 1500 to 1800 calories/day for men, or calculate how many calories that particular patient eats on daily basis and prescribe 500 to 750 fewer calories/day; or prescribe an evidenced-based diet that restricts certain food types (*eg*, high-carbohydrate, low-fiber, or high-fat foods), to create energy deficit by reducing food intake naturally

Physical activity recommendations: Centers for Disease Control and Prevention (CDC) recommend that PCPs can talk to patients about including either moderate-intensity (150 min/wk of walking, biking, swimming) or vigorous-intensity (75 min/wk of more strenuous activity) exercise; also muscle training, muscle strengthening, >2 days/wk working all major muscle groups; burning calories through physical activity, combined with reducing caloric intake, creates calorie deficit resulting in weight loss; most weight loss occurs via decreased caloric intake, but evidence shows weight loss can be maintained only through engaging in regular physical activity; studies from 1989 showed that *combining exercise with diet* produces optimal weight loss at 12 mo and best follow-up maintenance weight loss at 30 mo

Examples: *moderate intensity* — walking briskly 3 mph or faster (but not race walking) water aerobics, bicycling <10 mph, doubles tennis, ballroom dancing, general gardening; *vigorous intensity* — race walking, jogging or running, swimming laps, singles tennis, aerobic dancing, bicycling ≥10 mph, jumping rope, heavy gardening (*eg*, digging, hoeing), hiking uphill with a heavy backpack

Outcomes: although 3% to 5% weight loss in 3 mo is considered successful (usually 5% at 3 mo), initial weight loss predicts ultimate success; demonstrated by Look AHEAD study, in which patients with type 2 diabetes were put on lower-calorie diets and followed for ≤10 yr; those with intensive lifestyle who lost >10% at yr 1 were most likely to keep ≥5% of their weight loss at yr 4; of those who lost between 5% and 9.9% of their weight at yr 1, 40% achieved >5% weight loss at yr 4; of those who lost <5% at yr 1, 22% were able to lose 5% or maintain by yr 4; *adherence* to diet, not diet itself, predicts success; study by Dansinger in *JAMA* 2005; patients were put on 4 kinds of diets — Atkins, Zone, Weight Watchers, Ornish; followed those 4 arms over 12 mo and found diet type did not matter; ~25% of patients in each arm lost 5% to 10% and kept weight off at 12 mo

Regimens: *10-yr data from National Weight Control Registry* — published by Rena Wing and Jim Hill; showed what type of regimen predicts successful long-term weight loss; 10,000 subjects eligible to register if they had maintained ≥50-lb weight loss for 5 yr; average weight loss was 33 kg for 5 yr; ate 1800 calories/day (27% fat); performed exercise burning 2700 calories/wk (~30 min/d of vigorous walking); 40% weighed themselves daily, 20% weekly; reduced level of TV watching relative to average American; limited diet variety; 78% ate breakfast; ate fast food only 1x/wk and used more artificially sweetened beverages than others of normal weight; vigilant; this dataset shows that doing those things can be key to successful long-term weight loss

Behavioral modification: *5 As of behavioral modification* — *A*ssess, *A*dvise, *A*rrange, *A*gree, *A*ssist; important for many different modalities (*eg*, alcohol withdrawal) but have also been used in weight loss and weight maintenance; in weight-loss intervention, 5 As are: *Ask* patient if okay to talk about their weight; *Advise* — provide specific information about health risks and benefits of change (weight loss and maintenance as well as changing lifestyle); *Assess* patient's beliefs, behavior, and knowledge of lifestyle change; *Assist* in identifying barriers, strategies, problem-solving techniques, and social-environmental support; *Arrange* specific plans for follow-up visits, phone calls, and how patients can stay on their plan with follow-up from PCP; 5 As are geared toward developing personal action plans, using specific goals and behavioral terms and listing barriers and strategies

Motivational interviewing: can help with process of behavioral modification; patient-centered counseling style that seeks to elicit internal motivation to change behavior and encourage patients to understand and resolve ambivalence about behavior change; need to assess patient's readiness to change; other factors involved in gaining weight and ambivalence toward weight loss and weight maintenance include societal factors, stress at home and/or work, psychological issues; motivational interviewing can help "tease out" these factors

Readiness for change: important to determine a patient's readiness for change at beginning of first visit for weight loss or when you assess patient and determine if obese based on BMI and waist circumference; initiating change when patients not ready often leads to frustration and may hamper future efforts; using patient-centered, collaborative approach for behavior change can help patient identify their ambivalence; this approach more likely to succeed at combating complex psychological, physiological, and cultural forces that contribute to overweight or obesity

Readiness to change scale: assess patients and determine if they are in precontemplation, contemplation, preparation, action, maintenance, or relapse; usually, patients will be in precontemplation or contemplation mode; need to help them get to preparation, action, and maintenance; follow up to make sure you address relapse; for patients who are in contemplation, discuss diet, physical activity, lifestyle change, need for pharmacotherapy, and, if appropriate candidate, bariatric surgery

Pharmacotherapy

Overview: drug-treatment criteria based on BMI; patient with BMI either 30, or >30 with no comorbidities is eligible for pharmacotherapy; patient with BMI >27 with ≥1 comorbidity also eligible for a pharmacotherapy; recommendations are for adults — insufficient data for adolescents and children to create pharmacologic management guidelines

Guideline recommended to discuss pharmacologic management of obesity published in *Journal of Clinical Endocrinology and Metabolism* in 2015 by Apovian et al; covers options for medications for chronic weight management as well as medications that should be avoided or changed because they cause weight gain

Mechanisms of action: work in hypothalamus; area in arcuate nucleus with 2 sets of neurons; POMC/CART neurons cause satiety when activated; neuropeptide Y (NPY) agouti-related protein neurons cause hunger; most antiobesity medications work in arcuate nucleus; 7 medications used for obesity, 6 of which cause appetite suppression

Antiobesity agents: *phentermine* — approved in 1959; norepinephrine-releasing agent; works in hypothalamus; *diethylpropion* — norepinephrine-releasing agent, similar to phentermine; *lorcaserin* — 5-HT2C receptor agonist; long-term agonist for long-term use; phentermine and diethylpropion approved in 1959 for 3 mo of use; lorcaserin and others approved for long-term use; *liraglutide* — glucagon-like peptide-1 (GLP-1) agonist, the only antiobesity drug not an oral agent (injection only); *orlistat* — pancreatic and gastric lipase inhibitor; does not enter CNS or bloodstream; blocks of some fat absorption (~25% to ~30% of fat calories); only drug with this mechanism of action; others are appetite suppressants

Combination drugs: *phentermine* + *topiramate* — GABA receptor modulator + norepinephrine-releasing agent; *naltrexone* + *bupropion* — reuptake inhibitor of dopamine and norepinephrine + opioid antagonist

Advantages and disadvantages: phentermine and diethylpropion have been marketed for some time; generic, less expensive; adverse-event (AE) profile is downside; can cause elevated heart rate, anxiety, palpitations, insomnia; combination of topiramate + phentermine has robust data, as do others; data are more robust than for phentermine + diethylpropion; can be more expensive because branded drug; topiramate is teratogenic and should not be given to women who are pregnant or plan to be; none of these drugs should be given during pregnancy; lorcaserin has good AE profile; can be expensive; naltrexone + bupropion has particular effect on bingeing and food addictions; good long-term data; AE profile can be problematic — both drugs can cause elevated blood pressure; liraglutide has good AE profile; injectable, which can be downside for some patients; can be expensive; orlistat available both over-the-counter (OTC) and by prescription, but AE profile can be problem for some patients

Efficacy and safety: if loss of >5% of body weight at 3 mo and medication is safe and tolerated by patient, it can be continued; deemed to be effective and safe; if loss of <5% of body weight in 3 mo, or if safety and tolerability issues, choose another medication or another approach to weight loss

Selecting a medication: no precision medicine yet for obesity; many different kinds of obesity, complex disease; match weight-loss medications to patient profile (*ie*, why you would not give patient a certain medication); do not give phentermine, diethylpropion, or naltrexone + bupropion combination to patients with uncontrolled hypertension, history of cardiac disease, arrhythmia, or seizures; good choice for that patient would be lorcaserin; with individual with obesity who is taking an SSRI or SNRI for depression, do not choose lorcaserin because of potential for serotonin syndrome; better choice for that patient would be phentermine, topiramate, or phentermine alone; orlistat is likely safe for all individuals, since it does not enter bloodstream

Follow-up: frequent patient follow-up is key for lifestyle change, diet, exercise, and medications; Centers for Medicare and Medicaid Services (CMS) cover 15 visits/yr: 4 visits (1/wk) in mo 1; 1 visit/mo in mo 2 to 6; if loss of ≥3 kg, also cover 1 visit/mo in mo 7 to 12

Bariatric Surgery

Criteria: higher risk for bariatric surgery than for pharmacologic treatment, because these are surgical procedures; criterion — BMI >40 with no comorbidities or BMI >35 with ≥1 severe obesity-associated comorbidity (*eg*, type 2 diabetes, hypertension, sleep apnea, metabolic syndrome)

Types of surgery: *laparoscopic band* (Lap-Band®) — some patients still eligible for, and some surgeons still do, this procedure, but performed less frequently now; *Roux-en-Y* gastric bypass and *laparoscopic sleeve gastrectomy* — current gold standards (Roux-en-Y more often performed); *biliopancreatic diversion with duodenal switch* — performed in some states in US

Weight-loss results: with Roux-en-Y gastric bypass, generally average weight loss of 32% to 33%; with laparoscopic sleeve gastrectomy, generally ~25% weight loss; weight loss much lower with laparoscopic band, ~≤20%; many surgeons elect not to do that procedure because of reoperation and complications; good long-term data on bariatric surgery; average of ~32% weight loss in first yr; average ~18% weight loss at 20 yr; in majority of cases, most weight kept off

Benefits: bariatric surgery reduces overall mortality and diabetes mortality by 88%; study by Adams et al in *The New England Journal of Medicine* in 2007; studied matched subjects, surgery group, and control group; reduction in all-cause deaths and deaths from diabetes in surgical group; systematic review and meta-analysis of procedures performed between 2003 and 2012, published in *JAMA Surgery*, concluded that bariatric surgery provides substantial and sustained effects on weight; ameliorates obesity-attributed comorbidities in majority of patients, most effectively for type 2 diabetes, but also for sleep apnea

Risks: mortality rate 0.08% in ≤30 days and 0.31% beyond 30 days; complication rate ~17% and reoperation rate ~7%; risks of complications, reoperations, and mortality exist

Effectiveness: Roux-en-Y gastric bypass more effective surgery for weight loss; more complications compared with adjustable gastric banding in sleeve gastrectomy; adjustable gastric band has lower mortality and complication rates than the other 2, but higher reoperation rate and less weight loss than gastric bypass and sleeve gastrectomy; sleeve gastrectomy also effective for weight loss and comparable in some respects to gastric bypass

Pre- and postoperative care: important to have a pre- and postoperative care protocol

- American College of Endocrinology (ACE) guidelines for pre- and postoperative care of bariatric surgery patients recommend multidisciplinary approach
- Healthy eating, education by registered dietician; vitamins and minerals for pre- and postoperative patients include vitamin D, vitamin B12, multivitamins, calcium citrate
- Protocols stress adequate hydration, especially postoperatively; monitoring of blood glucose and reduction in diabetes medications postoperatively in patients with diabetes; long-term follow-up
- Short-term follow-up: usually every 3 mo, including lab work, for 1 yr postoperatively; thereafter, at least yearly, including lab work indefinitely; surgery and medication can produce better long-term weight loss; some patients regain weight even after bariatric surgery; emerging studies show early adoption of medications in patients who experience weight regain can restore weight loss and ensure weight maintenance

Suggested Reading

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Pituitary, Adrenal, and Thyroid Disease

John Carmichael, MD, *Associate Professor of Medicine and Co-Director, USC Pituitary Center, Keck School of Medicine of the University of Southern California, Los Angeles, CA*

Pituitary gland: 5 main cell types; *somatotropes* — secrete growth hormone; *lactotropes* — secrete prolactin; *corticotropes* — secrete ACTH; *gonadotropes* — secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH); *thyrotropes* — secrete thyroid-stimulating hormone (TSH); each hormone enters circulation and affects receptors at end organs; all except prolactin part of negative feedback loop; cortisol secreted by adrenal gland in response to adrenocorticotropic hormone (ACTH), then feeds back to hypothalamus and pituitary to regulate ACTH secretion from pituitary; gonadotropes under negative feedback by sex steroids (estrogen and testosterone); thyrotropes under negative feedback by thyroid hormone; lactotropes under tonic inhibition by neuropeptide dopamine to help suppress prolactin secretion

Hypopituitarism: partial or complete deficiency in any pituitary hormone and its secretion; incidence 4.2 per 100,000 persons; prevalence 45 per 100,000 persons; statistics may be underestimated because some cases associated with traumatic brain injury not included; main causes of pituitary failure relate to pituitary tumors and their treatment; most pituitary dysfunction or hypopituitarism results from compressive effects of pituitary tumor, pituitary tumor surgery, or radiation

Pituitary apoplexy: cause of acute hypopituitarism; characterized by sudden pituitary hemorrhage and infarction, causing sudden headache, visual changes (*eg*, double vision, acute blindness), third-nerve or sixth-nerve palsy, ophthalmoplegia, nausea, vomiting, altered mental status

Postpartum hemorrhage (Sheehan syndrome): causes infarction of enlarged normal pituitary gland; presents as inability to lactate and lack of resumption of menstruation

Lymphocytic hypophysitis: infiltration of pituitary with lymphocytes; presents with postpartum headache and hypopituitarism; predilection toward adrenal axis (adrenal insufficiency only)

Pituitary tumor: presents with mass effects of bitemporal hemianopsia, headache, nonspecific symptoms

Typical patterns of pituitary hormone loss: help establish diagnosis of hypopituitarism; pituitary tumors have early effects on growth hormone and gonadotropins with later compressive features (*eg*, central hypothyroidism, adrenal insufficiency); *clinical pearl* — if premenopausal patient has regular menstrual periods, implies intact, functional pituitary

Clinical manifestations of pituitary failure:

Acute apoplexy: greatest concern for mass effect and acute adrenal insufficiency; presents with weakness, nausea, vomiting, hypotension; needs immediate treatment; other pituitary axes do not manifest acutely; no acute gonadal or thyroid failure; enough circulating thyroid hormone in acute setting

Longstanding growth hormone deficiency: in adults, symptoms nonspecific, typically similar to natural aging process; increased central adiposity, decreased cognitive function and muscle mass

Longstanding gonadal failure: impaired libido in men, loss of menses and infertility in women; no clinical presentation in postmenopausal women

Longstanding central hypothyroidism: like primary hypothyroidism; fatigue, constipation, bradycardia, nonspecific findings

Longstanding adrenal insufficiency: weight loss, fatigue, loss of appetite; hypotension, especially when going from sitting to standing

Diagnosis: need to investigate each axis separately

Adrenal insufficiency: ACTH and cortisol measurement may be helpful, but usually does not give clear diagnosis; ACTH and cortisol have diurnal and pulsatile secretory pattern; measurements often in indeterminate range; random measurement of cortisol level in morning (>18 mcg/dL rules out adrenal insufficiency, <3 mcg/dL highly suggestive but not diagnostic, between 3 mcg/dL and 18 mcg/dL requires dynamic test of cortisol or ACTH secretion); several dynamic tests (some easier to perform than others); insulin tolerance tests (never performed in acute adrenal insufficiency) require insulin infusion and hypoglycemia to diagnose; metyrapone testing cuts off adrenal production of cortisol and causes elevated cortisol precursor; *ACTH stimulation test using synthetic truncated ACTH* — most common test of adrenal insufficiency; can be done to investigate central adrenal insufficiency only after sufficient time has passed to allow for adrenal atrophy; 4 wks to 6 wks without ACTH causes adrenals to decrease cortisol secretion so testing can occur; treat first, test later

Thyrotrope assessment: need to measure both serum TSH and thyroxine (free thyroxine best first test); serum TSH normal in most cases of central hypothyroidism, but inappropriately normal compared with T_4 level; T_4 level in central hypothyroidism low and TSH usually inappropriately normal; *clinical pearl* — TSH measurement not helpful in diagnosis and management of central hypothyroidism because

TSH has reduced bioactivity in presence of pituitary tumors

Gonadal axis: depends on sex and age; postmenopausal women have decrease in LH and FSH inappropriate for postmenopausal state (can help determine if any pituitary damage) but may have no symptoms; in premenopausal women, menstrual history more important than measuring LH, FSH, or estradiol; in adult males, basal testosterone, LH, and FSH measurement in morning with >1 sample best method to detect hypogonadotropic hypogonadism

Growth hormone deficiency: low insulin-like growth factor (IGF-1) suggests deficiency, but most adult patients require dynamic growth hormone testing

Treatment: hydrocortisone or another glucocorticoid for patients with adrenal insufficiency; stress dosing needed when undergoing procedures or with febrile illness; central hypothyroidism treated with replacement levothyroxine; gonadal replacement with testosterone for men; in premenopausal women, replace estrogen and progesterone if uterus intact; most postmenopausal women do not require estrogen therapy; growth hormone replaced if growth hormone deficiency present; *clinical pearl* — after diagnosis of hypopituitarism or hyperprolactinemia, order pituitary magnetic resonance imaging (MRI)

Pituitary tumors: benign tumors that arise from anterior pituitary; classified based on what cell type derived from and by size; microadenomas <10 mm in diameter; macroadenomas ≥10 mm in diameter; further classification by cell type (hormone produced) but can be nonfunctional; somatotroph tumors cause acromegaly with growth hormone excess; prolactinomas derived from lactotrope cells, cause excessive prolactin secretion; corticotroph adenomas secrete ACTH to cause Cushing disease; rarely, thyrotroph cells cause adenomas that secrete TSH; most common tumors gonadotroph tumors, silent (do not cause syndromes of excessive testosterone or estrogen production); presentation includes mass effects, hypopituitarism signs, headaches, and visual disturbances; classic finding bitemporal hemianopsia; functional tumors have classic physical examination and laboratory findings

Prolactinomas among most common pituitary adenomas (especially in premenopausal women); present with galactorrhea and amenorrhea; next step, order serum prolactin level (>200 ng/mL diagnostic)

Somatotroph adenoma: patients with acromegaly present with enlarged hands and feet, underbite, frontal bossing, increased spacing of teeth, and profuse sweating; best test serum IGF-1; if borderline values, oral glucose tolerance test with growth hormone measurement (usually suppresses after glucose load but fails to suppress in acromegaly)

Cushing disease: patients typically present with proximal muscle weakness, characteristic facial features (moon face), central adiposity, dystrophic fat deposition in cervical and supraclavicular region, wide purple striae, and comorbidities of diabetes mellitus and hypertension; next-best tests screening tests (*eg*, 24-hour urine measurement of cortisol secretion, late-night salivary cortisol level by either saliva or plasma); after high cortisol level established, obtain ACTH level to determine if ACTH-dependent; most ACTH-dependent hypercortisolemia results from corticotroph adenoma causing Cushing disease

Other things to be aware of:

Physiologic enlargement may mimic tumor toward end of pregnancy or in longstanding primary hypothyroidism as reaction to lack of thyroid hormone

Incidental pituitary tumors common; workup varies; prolactin and IGF-1 should be measured to detect early acromegaly; if large tumor, check for hypopituitarism

Familial syndromes including pituitary tumors: unusual; multiple endocrine neoplasia type 1 (MEN1) causes hyperparathyroidism, primary hyperparathyroidism, pituitary tumors, and pancreatic neoplasia; screening if positive family history or calcium elevation in patient with pituitary tumor

Evaluation: prolactin level single most important blood test; *clinical pearl* — next-best test after detecting pituitary adenoma if prolactin level not tested; crucial because result changes management; prolactinomas treated medically while all other pituitary tumors treated surgically; small tumors monitored with observation rather than treated immediately; surgery treatment of choice for growth hormone-, ACTH-, and TSH-secreting tumors, and for nonfunctioning pituitary adenomas causing mass effect with visual-field deficits; surgery also treatment of choice for prolactinomas not responsive to dopamine agonists

Physiologic (nontumor) causes of prolactin elevation: medications major cause of nontumor elevations; most commonly psychotropic agents (*eg*, risperidone [Risperdal], other early typical antipsychotic agents); prolactin can be elevated in pregnancy, so pregnancy test should be ordered on all women with prolactin elevation; once prolactinoma diagnosed, dopamine agonist (*eg*, cabergoline [Dostinex], bromocriptine [Cycloset, Parlodel]) can be used for symptomatic treatment to reverse visual-field deficits, infertility, other aspects of hypogonadotropic hypogonadism, or galactorrhea

Diabetes insipidus: inability to concentrate urine because of vasopressin insufficiency (central diabetes insipidus) or vasopressin resistance at level of kidney (nephrogenic diabetes insipidus); almost never presentation of anterior pituitary tumors, but commonly seen after surgery or head trauma; *typically presents as part of triphasic response* — 1. transient diabetes insipidus; inability to concentrate urine, high volume urine output, increased thirst, and predilection for cold liquids; 2. syndrome of inappropriate antidiuretic hormone secretion (SIADH) that usually lasts 7 days postoperatively; 3. diabetes insipidus; most cases, however, resolve back to normal

Thyroid

Hyperthyroidism: terminology sometimes confusing; thyrotoxicosis, any form of thyroid hormone excess (including taking exogenous thyroid hormone to excess); hyperthyroidism implies that thyroid responsible for excess thyroid hormone; *4 main forms of hyperthyroidism* — 1. Graves disease; autoimmune stimulation of thyroid hormone release and multinodular goiters that can become toxic and cause hyperthyroidism; 2. autonomous nodules (hot nodules); 3. destructive (subacute thyroiditis); silent and painless; and 4. postpartum thyroiditis

Signs and symptoms: palpitations, increased sweating, weight loss, hyperdefecation, anxiety, tachycardia, tremor, smooth skin, and hyperreflexia; classic eye finding of proptosis or stare (may be exhibited by lid lag)

Evaluation: first test serum TSH, then thyroxine (usually free thyroxine) level; may need to order triiodothyronine (T_3) level to determine if preferential secretion of T_3 from toxic nodule (rare, check if suppressed TSH and normal free T_4)

Thyroid function tests: Graves disease and other forms of primary hyperthyroidism present with suppressed TSH and elevated free T_4; toxic adenoma may present with suppressed TSH, normal free T_4, and elevated T_3; subclinical hyperthyroidism presents with suppressed TSH (below lower normal limit but still detectable), normal T_3 and T_4, and no symptoms; thyrotoxicosis with elevated TSH may result from hyperthyroidism secondary to TSH-secreting pituitary adenoma (rare)

Thyroid uptake and scan: uses radioactive iodine to determine if clinical presentation results from high–iodine-uptake state; Graves disease will take up lot of iodine and cause hyperthyroidism; other forms (subacute, postpartum, or painless thyroiditis) low–radioactive iodine–uptake states and typically no scan ordered because nothing to visualize with low uptake; can also help differentiate between other forms of hyperthyroidism; patchy uptake in patients with toxic multinodular goiter; focal uptake in half of gland with toxic adenoma

Antibody levels: may be helpful; thyroid peroxidase antibodies elevated in autoimmune processes; elevated thyroid-stimulating immunoglobulin or thyroid receptor antibodies pathognomonic for Graves disease (antibodies elevated)

Thyroid storm: severe presentation of hyperthyroidism characterized by cardiac decompensation, fever, severe forms of other symptoms of hyperthyroidism, and altered mental status

Treatment: medical therapy; can also include radioactive iodine therapy or thyroid surgery; choice depends on presentation; most patients treated initially with antithyroid drugs (methimazole [Tapazole, Northyx] or propylthiouracil [PTU]) and beta blockers to decrease disease manifestations; patients with destructive thyroiditis may not require antithyroid medication but may benefit from anti-inflammatory medication for neck pain and beta blockers for disease manifestations; for toxic adenoma or multinodular goiter with thyrotoxicosis, consider patient preference for medical, surgical, or radioactive iodine therapy; *Graves disease* — because radioactive iodine may worsen proptosis in patients with severe Graves eye disease, treat with glucocorticoids beforehand or choose another mode of therapy; pregnant patients require PTU during first trimester and methimazole thereafter; Graves disease may improve during pregnancy; *subclinical hyperthyroidism* — may be treated with methimazole when TSH suppressed below 0.1 mcIU/mL; *thyroid storm* — usually treated with PTU or methimazole, but glucocorticoids may be needed; patients often treated with beta blockers (propranolol [Hemangeol, Inderal, InnoPran XL] preferred); iodine treatment may slow and improve thyroid storm; agranulocytosis, important idiosyncratic adverse effect of methimazole or PTU treatment; complete blood count (CBC) not warranted, but patients should stop medication if they develop fever or sore throat (if so, obtain CBC)

Hypothyroidism: most common causes include Hashimoto thyroiditis (chronic lymphocytic thyroiditis) as well as secondary to previous radioactive iodine treatment, thyroidectomy, or external beam radiation (*eg*, for lymphoma treatment)

Signs and symptoms: fatigue, lethargy, cold intolerance, constipation, weight gain, menstrual irregularity, and nonspecific symptoms (so thyroid function testing needed to confirm diagnosis); physical examination shows dry skin, brittle hair, nail changes, bradycardia, delayed relaxation phase of deep tendon reflexes

Evaluation: thyroid function testing; elevated TSH, low free T_4; thyroid peroxidase antibodies to determine if secondary to autoimmune phenomenon (Hashimoto thyroiditis); subclinical hypothyroidism characterized by lack of symptoms or nonspecific symptoms, coupled with mild TSH elevation and normal T_4 levels; nonthyroidal illness can alter thyroid function testing results and confuse diagnosis of hypothyroidism; testing shows low or normal free thyroxine with low, normal, or elevated TSH; typically resolves on its own

Treatment: replacement with levothyroxine (*eg*, Levothroid, Synthroid, Unithroid); guided by periodic measurement of TSH to target normal range and adjust medication; myxedema coma with severe hypothyroidism (severe hypothermia, hypotension, and bradycardia; usually precipitated by some other medical illness) may require loading with high-dose levothyroxine; if subclinical hypothyroidism (normal thyroxine and mild TSH elevation), treat patients anticipating pregnancy or have TSH <10 mcIU/mL; *clinical pearl* — thyroid uptake and scan not helpful

Thyroid nodules: main concern, rule out thyroid cancer; very common, found incidentally with ultrasounds or computed tomography (CT) scans; patients may or may not be aware of them

Evaluation: thyroid function testing; nodules typically nonfunctional, so if hyperthyroidism present, perform thyroid uptake and scan (not fine-needle aspiration); if normal thyroid function, ultrasound to determine size and characteristics to determine risk of malignancy; large nodules (>1 cm) and those with irregular borders or calcifications (indicative of possible psammoma bodies associated with papillary thyroid cancer) should be biopsied; if multiple nodules or multinodular goiter, perform same workup for thyroid cancer

Management: if thyroid cancer diagnosis or high suspicion, thyroidectomy or partial thyroidectomy depending on nodule size; most nodules benign on fine-needle aspiration, so periodic ultrasound used to monitor for increasing size, which would prompt further evaluation and additional biopsy; large thyroid nodules or multinodular goiter may cause compressive symptoms of dysphagia or dyspnea with exertion; very large goiters may cause thoracic outlet obstruction and require surgical evaluation for possible thyroidectomy

Adrenal Glands

Adrenal incidentalomas: >1 cm; found incidentally on imaging studies for nonadrenal disease; prevalence

ranges from 0.5% to 10% in imaging studies (higher in autopsy studies); bilateral masses in 10% to 15% of cases; 2 main concerns, malignancy and functionality (most patients asymptomatic, though); approach toward mass based on size and imaging characteristics; size >6 cm more likely to be malignant, <4 cm typically benign; controversy about management of lesions 4 cm to 6 cm; primary adrenal malignancy uncommon (~2%-5% of adrenal incidentalomas); secondary metastasis from known primary (~0.5%-2.5%); using 4-cm cutoff point at time of diagnosis has ~93% sensitivity and limited specificity (~76% of lesions >4 cm benign)

Evaluation:

Imaging phenotype: CT or MRI scans; *CT phenotype* — lipid-rich tumors usually benign, measured on CT by Hounsfield units; precontrast Hounsfield unit score <10 implies benign adenoma; adrenocortical carcinomas have high CT-scan attenuation, with Hounsfield unit score >20); smoothness of borders tends to tell whether benign or malignant; rapid contrast washout typically associated with benign adenomas; myelolipomas (benign adrenal nodules) have very low Hounsfield unit score (<–40, typically unique score and specific to myelolipomas), generally managed by observation; *clinical pearl* — adrenal adenoma with Hounsfield unit score <–40 benign and requires only observation; pheochromocytomas present area of overlap between benign adenomas and adrenocortical carcinoma or metastases because can have Hounsfield unit score >20, so important to look at other features and secretory pattern to differentiate; *MRI phenotype* — malignancies have rapid gadolinium uptake and marked enhancement with slow washout; rapid washout associated with benign adenomas; on chemical-shift MRI, benign adenomas lose signal on out-of-phase images, but bright on in-phase images

Hormonal evaluation: 2 main tests, 1-mg overnight dexamethasone suppression test for hypercortisolemia and 24-hr urinary metanephrines and catecholamines for pheochromocytoma; in patients with hypertension or hypokalemia, check plasma aldosterone concentration and plasma renin activity to determine ratio as screen for hyperaldosteronism; if positive results or suspicion of positivity, follow up with further testing; in these patients, long-term follow-up if negative testing, every 6 mos to 12 mos and imaging every 6 mos to 12 mos to check for growth or changes

Hypercortisolism (Cushing syndrome): characteristic features include facial fullness and plethora, supraclavicular fullness, dorsocervical dysplasia; most specific facial plethora, proximal muscle weakness, wide (>1 cm) purple striae, easy bruising; less-specific features include obesity, dorsocervical dysplasia, and facial fullness (also present in general population)

Evaluation: screen for Cushing syndrome with >1 test (different modes); 1-mg overnight dexamethasone suppression test (also used for adrenal incidentalomas); 24-hr urinary cortisol collection; late-night salivary cortisol level (instead of admitting patients for nighttime serum cortisol measurement); these 3 screening tests can provide biochemical evidence of hypercortisolemia; if hypercortisolemia believed to result from excessive cortisol secretion, not physiologic reaction to alcohol abuse, obesity, or extreme depression, proceed to work up for ACTH-dependent vs ACTH-independent cause; measure ACTH; low or suppressed ACTH indicates adrenal cause; inappropriately normal or elevated ACTH indicates pituitary, but may need to rule out ectopic ACTH source; if ACTH inappropriately elevated, get pituitary MRI; if ACTH suppressed or undetectable, get adrenal CT to evaluate potential adrenal causes

Treatment for adrenal sources of hypercortisolemia (benign adrenal adenomas, adrenal carcinomas, multinodular disease in adrenals): surgical resection; effective treatment causes adrenal insufficiency that requires replacement until recovery of HPA axis

Pheochromocytoma: rare tumor arising from adrenal medulla; hormonally active in secreting norepinephrine, epinephrine, or dopamine; diagnose by measuring neuropeptides and/or their metabolites; typical presentation includes hypertension, headache, excessive sweating, flushing, "spells," orthostatic hypotension from volume depletion

Evaluation: assessment of urine or plasma; if low suspicion, urinary measurement of metanephrines and catecholamines and fractionated measurements of those; plasma fractionated metanephrines preferred if high degree of suspicion (*eg*, family history, possible syndrome associated with pheochromocytoma or paraganglioma such as MEN2, von Hippel-Lindau disease, or neurofibromatosis); positive results usually 2 to 4 times upper limit of normal; follow up positive results with MRI or CT of abdomen and pelvis; for further clarification functional scan with metaiodobenzylguanidine (MIBG) scan can help localize hypersecretion

Treatment: crucial to pretreat with alpha blockade, followed by beta blockade, to control blood pressure; patients instructed to hydrate well and even salt load before interventions; surgery to remove pheochromocytoma

Primary hyperaldosteronism: fairly common in patients with hypertension (14% have aldosterone elevation); secondary to aldosterone-producing adenoma or bilateral adrenal hyperplasia; typical presentation of difficult-to-control hypertension, hypokalemia, and metabolic alkalosis (only about one-third) have hypokalemia, but few have hypokalemia without hypertension)

Evaluation: simultaneous measurement of plasma aldosterone concentration and plasma renin activity; 2 *diagnostic criteria* — plasma aldosterone concentration to renin ratio>20 plus plasma aldosterone concentration level >15, suggests primary hyperaldosteronism; after screening, confirm by attempting to suppress aldosterone concentration in response to high salt load (oral or intravenous [IV]); patients able to suppress <5 ng/dL do not have primary hyperaldosteronism, those who do not suppress do have it; next, consider adrenal vein sampling if source of hyperaldosteronism unclear; tricky because 1 adenoma would be sufficient in younger patients, but higher frequency of nonfunctional benign adenomas in older patients; adrenal vein sampling in older patients usually required to confirm which side to operate on; if high chance for cure, can approach surgically; if bilateral adrenal hyperplasia or patient not surgical candidate, medical therapy with spironolactone (Aldactone,

CaroSpir) or eplerenone (Inspra) to control hypertension and hypokalemia

Adrenal insufficiency: can be primary (resulting from some defect in adrenal gland secretion) or secondary (either pituitary or hypothalamus not stimulating adrenal secretion); most common causes include autoimmune adrenal insufficiency (Addison disease), in which patients typically have other autoimmune diseases (*eg*, type 1 diabetes mellitus, primary hypothyroidism, vitiligo); secondary adrenal insufficiency most commonly seen in patients with longstanding glucocorticoid use followed by withdrawal; key difference between primary and secondary, in patients with secondary adrenal insufficiency, typically only cortisol secretion affected, and renin-angiotensin-aldosterone system intact so they have milder hypotension; patients with primary typically lose function of cortisol and aldosterone secretion as well as adrenal androgens; patients may present with long history of fatigue, weight loss, hypotension, and hypoglycemia; those with primary adrenal insufficiency present with hyperpigmentation (not feature of central adrenal insufficiency); if anorexia or nausea, high degree of suspicion for adrenal insufficiency

Evaluation: morning serum cortisol measurement (when cortisol levels highest) <3 mcg/dL usually associated with adrenal insufficiency and >18 mcg/dL rules out adrenal insufficiency; values between 3 mcg/dL and 18 mcg/dL nondiagnostic; need stimulation test with cosyntropin (synthetic analog of ACTH); normal rise in cortisol to >18 mcg/dL to 20 mcg/dL; ACTH measurement can help determine if primary vs secondary; if morning ACTH elevated, adrenal CT scan; if adrenal insufficiency with low or inappropriately normal ACTH, perform pituitary MRI

Treatment: high-dose steroids (IV hydrocortisone or dexamethasone if associated with apoplexy, in which case treatment for edema also needed); important to treat prior to investigation, especially if acute adrenal crisis (acute hypotension with nausea and vomiting); longstanding replacement with hydrocortisone 2- or 3-times-daily dosing (10-30 mg/day); if primary adrenal insufficiency, use fludrocortisone as mineralocorticoid replacement

Review of Clinical Pearls:

Menstrual periods: good sign in premenopausal patients that overall pituitary function is intact; usually better than any testing to assess pituitary function in patients with pituitary tumors

Measurement of TSH in patients with pituitary tumors: typically normal and free thyroxine low in patients with central hypothyroidism; following TSH not helpful to determine dosing in patients with pituitary disease (in contrast to those with primary hypothyroidism)

Prolactin measurement: next step in evaluating pituitary tumor; one of most important tests to determine management

Myelolipoma: typically presents incidentally on adrenal CT scan; Hounsfield units <–40; management by observation

Suggested Reading

Charmandari E et al: Adrenal insufficiency. *Lancet.* 2014;383(9935):2152-67; **Heidelbaugh JJ:** Endocrinology update: hypopituitarism. *FP Essent* 2016;451:25-30; **Subekti I et al:** Current diagnosis and management of Graves' disease. *Acta Med Indones* 2018;50(2):177-82.

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Calcium and Bone Metabolism

Mike Lewiecki, MD, *Director, New Mexico Clinical Research in Osteoporosis Center; Director, Bone Health TeleECHO, University of New Mexico School of Medicine, Albuquerque, New Mexico*

Overview: skeleton contains 99% of the body's calcium stores as hydroxyapatite; ingested calcium is absorbed mostly in the duodenum and jejunum; daily calcium losses in GI tract amount to about 800 mg/day; urinary loss about 200 mg/day on average; inadequate calcium intake leads to increases in parathyroid hormone (PTH), which increases bone remodeling; serves to maintain serum calcium levels at constant levels by causing calcium loss from skeleton and increasing calcium absorption in gut; vitamin D plays important role in enhancing GI absorption

Serum calcium: normal range for total serum calcium is about 8.5 to 10.5 mg/dL; exact values vary by laboratory; about half is bound to albumin and biologically inactive; dehydration or hemoconcentration may elevate albumin levels and falsely elevate total serum calcium

Albumin-corrected serum calcium: when albumin levels fluctuate, this can be calculated by an adjustment of 0.8 for every 1.0 mg/dL variation in albumin from a normal estimated at 4.0 mg/dL; if albumin is 3.0 mg/dL and total serum calcium is 8.0 mg/dL, the albumin-corrected serum calcium would be 8.8 mg/dL

Calcium intake: National Osteoporosis Foundation *Clinician's Guide* recommends 1000 to 1200 mg/day of calcium, ideally from diet; recommended calcium for men aged 50 to 70 is about 1000 mg/day; 1200 mg/day recommended for women older than 50 and men older than 71; no evidence of benefit with intake greater than 1200 mg/day; some possible harm, primarily increasing risk of kidney stones; Institute of Medicine also recommends about 1000 to 1200 mg/day; upper limit of about 2000 mg/day; assumes adequate GI absorption of calcium; in calcium malabsorption, higher doses may be necessary

GI malabsorption: lecturer gives example of 65-year-old woman with screening dual-energy x-ray absorptiometry (DXA) femoral-neck bone density T score of −2.8, meeting WHO criteria for osteoporosis, and with 24-hour urinary calcium of 42 mg (lower limit of normal 50 mg) with normal calcium intake and renal function; celiac disease is a common cause of GI malabsorption in patients with osteoporosis even in absence of GI symptoms; patient's celiac antibody results were abnormal and small bowel biopsy was consistent with celiac disease; gluten-free diet resulted in improved calcium absorption and significant increase in bone-mineral density

Dietary calcium: dairy products are the commonest source; each serving has approximately 300 mg; fortified soy milk, almond milk, rice milk, and some orange juice preparations are also good sources; in addition, individuals typically get about 250 mg/day from nondairy sources

Calcium supplements: if patient is unable to get adequate daily intake from diet, calcium supplements may be necessary; two large groups, calcium carbonate and calcium citrate; fractional absorption of calcium carbonate is about 30%; about 40% for calcium citrate; calcium carbonate requires gastric acid for good absorption; probably best to take with food; calcium citrate can be taken independently of meals; advisable to take no more than 500 to 600 mg at one dose; larger amounts are not well absorbed

Constipation: calcium preparations can cause constipation in some patients, another reason dietary calcium is preferable; adding magnesium, which has laxative effect, may help counteract

Daily value: on product labels, daily value (DV) is used; must be converted to mg to make interpretable for patients; simple way to do that is to add a zero to the daily value; a product with 30% DV of calcium on the label contains 300 mg

Vitamin D

Intake: National Osteoporosis Foundation *Clinician's Guide* recommends intake of 800 to 1000 IU/day with target of at least 30 ng/mL for blood level of serum 25-hydroxyvitamin D; Institute of Medicine recommends slightly lower daily intake in the range of 600 to 800 IU with a target level of >20 ng/mL; suggests upper limit of 4000 IU/day

Absorption: some patients absorb vitamin D less well than others; some metabolize vitamin D differently; amount of vitamin D intake required in an individual to maintain adequate serum level may be variable; most clinical organizations suggest serum 25-hydroxyvitamin D target range of about 30 to 50 ng/mL

Deficiency: often defined as less than 20 ng/mL; measure serum 25-hydroxyvitamin D and not 1,25-dihydroxyvitamin D, which is not as good a representation of total vitamin D stores; routine screening not recommended, but is often good idea to evaluate vitamin D level in patient with osteoporosis where treatment is anticipated

Dietary sources: few good dietary sources; vitamin D fortified milk can provide some; approximately 400 IU per quart; some juices and some cereals are fortified with vitamin D; saltwater fish, liver, and cod liver oil contain vitamin D and may be beneficial in some patients

Causes of low levels: low vitamin D levels are common; associated with factors such as limited sun exposure, use

of sun block, use of protective clothing, having dark skin pigment, and living at high latitude; some antiseizure medications can increase metabolism of vitamin D; malabsorption may occur from GI diseases; patients with chronic kidney disease and obesity may have low levels

Treatment: can usually use over-the-counter products; available as vitamin D3 or vitamin D2; both probably fine, although D3 may be slightly preferable; pharmacological doses are rarely needed, except in cases of symptomatic vitamin D deficiency, where patients may have bone pain related to osteomalacia; supplementation with 1000 IU/day is expected to increase serum 25-hydroxyvitamin level by approximately 8-10 ng/mL over about three months; great variability in response; wait at least three months for a new steady state to be achieved with a steady dose, then titrate to achieve desired level; remind patients that they need to continue supplementation; often patients will take supplementation for a period of time, think their problem is corrected, and stop supplementation

Hypercalcemia

Overview: defined as an albumin-corrected serum calcium greater than the upper limit of normal for the laboratory used; frequently no symptoms when hypercalcemia is of slow onset and mild; symptoms, especially with very high levels, include GI manifestations such as nausea, vomiting and constipation; neurologic manifestations may include confusion, lethargy and depression; fractures and kidney stones sometimes occur; patients may experience cardiac rhythm disturbances and palpitations; primary hyperparathyroidism is the most common cause of hypercalcemia in clinical practice; other possible causes include some cancers, sarcoidosis, and immobility

Evaluation: typically begins with measurement of serum intact PTH level; depending on clinical circumstances, may be helpful to measure a PTHrP (PTH-related peptide or protein); a 25-hydroxyvitamin D may be helpful; 1,25-dihydroxyvitamin D sometimes needed; with sarcoidosis, there is increased conversion of 25-hydroxy to 1,25-dihyroxy D, causing hypercalcemia; sometimes seen in cases of myeloma; serum protein electrophoresis may be helpful as a screening test for myeloma

Treatment: depends on cause; for primary hyperparathyroidism, there are well established indications for parathyroid surgery developed by International Workshop on Treatment of Asymptomatic Primary Hyperparathyroidism; surgery recommended if serum albumin-corrected calcium is greater than 1.0 mg/dL over upper limit of normal; if patient has osteoporotic T-score or significant decrease in bone mineral density; if patient has had a vertebral fracture, a creatinine clearance less than 60, kidney stones either clinically or by imaging such as renal ultrasound, or age less than 50 years

Hypocalcemia

Overview: defined as an albumin-corrected serum calcium less than lower limit of normal; hypoparathyroidism is most common cause; most often postsurgical; often occurs transiently after parathyroidectomy; another condition is pseudohypoparathyroidism; involves PTH resistance with low serum calcium and high PTH level in blood; severe vitamin D deficiency may sometimes cause low calcium levels; renal failure and acute pancreatitis are other possible causes

Symptoms: primarily forms of neuromuscular irritability, such as tetany, muscle cramps, and paresthesias; neuropsychiatric symptoms include anxiety, depression, and brain fog

Evaluation: measurement of PTH level, serum 25-hydroxyvitamin D, and serum magnesium level; serum ionized calcium level may be helpful;

Treatment: for acute, symptomatic hypocalcemia, treatment often is with IV calcium, such as IV calcium gluconate; chronic hypocalcemia can often be managed with oral calcium supplements; sometimes large vitamin D doses are required, such as vitamin D3; calcitriol, which is activated to vitamin D, may also be used; PTH replacement is also available

PTH 1-84: there is now a medication of human recombinant PTH 1-84; appropriate for patients with hypoparathyroidism that is not well controlled with calcium and vitamin D supplementations alone; indications for replacement with PTH 1-84 include a requirement for calcium replacement that exceeds 2500 mg/day or calcitriol more than 1.5 µg/day; consider for patients with hypercalciuria, renal stones, nephrocalcinosis, high kidney stone risk, creatinine clearance less than 60, hyperphosphatemia, and/or a calcium-phosphate product greater than 55; also consider if they have malabsorption or reduced quality of life related to hypocalcemia

Osteopenia and Osteoporosis

Overview: osteoporosis defined as skeletal disorder characterized by compromised bone strength, predisposing to increased risk of fracture; bone strength reflects the integration of two main features, bone density and bone quality; bone density is what we measure in clinical practice, typically with DXA; bone quality is much more difficult to measure in clinical practice; there are methods in clinical trials for assessing bone quality and some emerging clinical tools that may help in evaluating bone quality and making clinical decisions

Public health perspective: about 53,000,000 Americans have either osteoporosis or low bone mass, osteopenia; about a 50 percent lifetime risk for fracture in a white woman; increased morbidity and mortality associated with osteoporotic fractures, especially fractures of hip and spine; about 20% of hip fracture survivors require long-term nursing care; costs are considerable; estimated that direct healthcare expenses for osteoporosis-related fractures will be about $25 billion per year by 2025

Positives: improving awareness in physicians and patients; excellent diagnostic tools for detecting patients at high risk of fracture even before first fracture has occurred, typically with DXA testing with screening according to standard guidelines; there are fracture-risk assessment algorithms such as FRAX that estimate the 10-year probability of fracture; these values are incorporated into treatment guidelines; have effective and safe treatments for osteoporosis; have large selection of medications, many generic and inexpensive; have a better understanding of pathogenesis, leading to the identification of potential treatment targets; new treatments have been emerging; we have federal initiatives to improve care

Negatives: continues to be underdiagnosed and undertreated; about 80% treatment gap for osteoporosis; high-risk patients with fractures such as hip fractures

often do not receive treatment to reduce risk of a subsequent fracture

Problems with adherence: adherence generally poor after initiation of treatment; after one year, many patients, maybe half, are no longer taking medication; patients often have poor understanding of balance of expected benefits and possible risks with therapy; physicians sometimes lack time or skills to explain this balance

Quality of bone density testing: quality standards must be adhered to to achieve accurate and precise measurement; inaccurate measurements and incorrect reporting can sometimes lead to poor clinical decisions

Insurance: there are often restrictions on coverage of bone density testing, use of specific drugs, vitamin D testing, and measurement of bone turnover markers to assess rate of bone remodeling; bone turnover markers are laboratory tests that can measure activity of osteoblasts and osteoclasts; give idea of rate of bone remodeling, which may be correlated with rate of bone loss and fracture risk; have been Medicare cuts in DXA reimbursement, low Medicare reimbursement for office-based DXAs, often below cost; has led to closing of outpatient DXA facilities, thus limiting access to diagnostic services

Bone density testing: many organizations have developed indications for testing; National Osteoporosis Foundation and International Society for Clinical Densitometry suggest that all women age 65 years and older and all men age 70 years and older have a screening test; also recommend that younger postmenopausal women, perimenopausal women, and men age 50 to 69 should have a bone density test based on risk factor profile; consider testing if patients have risk factors for fracture such as cigarette smoking or family history of osteoporosis; in addition, adults with fragility fracture or a disease or condition associated with low bone mineral density or bone loss should be considered for testing; examples include vitamin D deficiency, use of a medication known to be harmful to bones, such as some anti-convulsant medications, chronic glucocorticoid therapy, aromatase inhibitor therapy; also consider for women with breast cancer or androgen deprivation therapy and men with prostate cancer

Classification: WHO has a classification according to bone mineral density expressed as a T-score; T-score is standard deviation difference between patient's bone mineral density and mean bone mineral density of a reference population divided by the standard deviation of reference population; normal T-score is −1.0 or higher; low bone mass or osteopenia is T-score between −1.0 and −2.5; osteoporosis is T-score of −2.5 or lower; severe osteoporosis is T-score of −2.5 or lower plus fragility fracture; this classification applies to postmenopausal women, perimenopausal women, and men aged 50 years and older

Severe osteoporosis: severe does not refer to how low the T-score goes below −2.5; requires a T-score of −2.5 or below and a fragility fracture; fragility fracture greatly increases risk of future fractures; demonstrates that bones are more fragile than normal

Z-scores: T-scores are not used in premenopausal women and men under age 50 years; we describe bone mineral density as a Z-score, not a T-score; Z-score is a representation of patient's bone mineral density compared to a mean reference population matched for age and sex; T-scores should never be used in children under age 20

Fracture risk: most women with a hip fracture have a T-score better than −2.5, ie, not in the osteoporosis range; reason is that there are many more women with osteopenia and normal T-scores than women with T-scores −2.5 or below; even though risk of fracture rises as bone density declines, if there are many more women with T-scores better than −2.5, then they are likely to have fractures in total numbers higher than those with T-scores −2.5 or below; if a patient has a hip fracture and T-score better than −2.5, it's likely that the patient still has fragile bones, that you can diagnose osteoporosis, and that they deserve aggressive treatment to reduce fracture risk

Diagnosis of osteoporosis: three criteria in the U.S., developed by the National Bone Health Alliance; presence of any one makes the diagnosis; 1) T-score −2.5 or below, as measured at the lumbar spine, the total hip, the femoral neck, or the 33% radius if measured, assuming that the patient has been evaluated for other factors that might cause low bone density and that these have been eliminated; 2) low-trauma fragility fracture of hip, regardless of bone mineral density, or low-trauma fracture of vertebra, proximal humerus, or pelvis, or in some cases distal forearm, with a T-score between −1.0 and −2.5; 3) major osteoporotic fracture probability by FRAX ≥20% or 10-year probability of hip fracture ≥3%

Vertebral fractures: it's important to look for these as they are important in diagnosis of osteoporosis and often not clinically recognized; most common type of osteoporotic fracture; only about one-third of vertebral fractures are clinically recognized; have serious consequences in terms of morbidity and mortality; highly predictive of future fractures of all types

Effects: may change diagnostic classification, assessment of fracture risk, and clinical management; if patient has T-score between −1 and −2.5 and vertebral fracture is detected, can change the diagnosis from osteopenia to osteoporosis; newly recognized vertebral fracture should increase the physician's estimate of future fracture risk and lead to initiating pharmacological therapy; a vertebral fracture is an indication for treatment regardless of bone mineral density

Spine imaging: conventional spine x-rays are one option; another is vertebral fracture assessment (VFA), a noninvasive method of diagnosing vertebral fractures by DXA; can be done at the same time that bone density is measured by DXA by obtaining a lateral image of the spine; provides patient convenience with point-of-service testing, lower cost, and lower radiation exposure than conventional x-rays

Indications for vertebral imaging: developed by National Osteoporosis Foundation and International Society for Clinical Densitometry; should be considered in women aged ≥70 and men aged ≥80 if T-score ≤−1.0 at lumbar spine, total hip or femoral neck, in women aged 65 to 69 and men aged 70 to 79 if T-score is ≤−2.5 at same skeletal sites; consider in postmenopausal women and men aged ≥50 who have specific risk factors for vertebral fractures, such as low-trauma fracture during adulthood (age ≥50), historical height loss of at least 1.5 inches or prospective height loss of at least 0.8 inches, or if there is recent or ongoing long-term glucocorticoid therapy

Height loss: determine historical height loss by asking patient the tallest they've been; compare with accurate height measurement with wall mounted stadiometer; prospective height loss refers to height loss measured in office at two different times

FRAX: used to assess fracture risk in untreated women and men aged 40 to 90; can be accessed at the FRAX website; available on current DXA software and as app for smartphones; inputs are femoral-neck bone mineral density, plus yes-or-no response to seven clinical risk factors; bone mineral density plus clinical risk factors predict fracture risk better than either alone; output is 10-year probability of major osteoporotic fracture and 10-year probability of hip fracture; the four types of major osteoporotic fracture are hip, clinically symptomatic spine, shoulder, or forearm fractures; does not include all osteoporotic fractures; risk of all or any osteoporotic fracture is probably approximately twice risk of major osteoporotic fracture

National Osteoporosis Foundation (NOF) Treatment Guidelines: initiate pharmacological therapy in postmenopausal women and men aged 50 and older when T-score is ≤−2.5 at femoral neck, total hip, or lumbar spine, or if there has been a hip fracture or vertebral fracture; vertebral fracture is defined as either a clinically symptomatic fracture or a morphometric fracture, (asymptomatic fracture detected by vertebral imaging); consider pharmacological therapy when T-score is between −1.0 and −2.5 at femoral neck, total hip, or lumbar spine, and FRAX 10-year probability of hip fracture is ≥3% or 10-year probability of major osteoporotic fracture is ≥20%

Additional testing considerations: evaluate for factors contributing to skeletal fragility before initiating pharmacological therapy; recommended laboratory tests include complete blood count to rule out, eg, myeloma in an anemic patient; blood chemistry, including creatinine, is needed as some osteoporosis medications are contraindicated in patients with very low renal function; measure serum calcium, as it would be inappropriate to start osteoporotic medication if serum calcium is out of normal range; phosphorus should be measured as least once, because some disorders resulting in low phosphorus can cause low bone density and may need to be treated differently from osteoporosis; for example, patients with tumor-induced osteomalacia may present with fractures and low bone density; diagnosis suggested by low phosphorus level; often caused by small tumor of mesenchymal origin; resection of tumor can cure the bone abnormality; serum albumin measurement needed for correction of serum calcium; high alkaline phosphatase can occur in cases of Paget's disease and metastatic bone cancer; low alkaline phosphatase may occur in rare metabolic bone diseases such as hypophosphatasia; abnormal liver enzymes may suggest chronic liver disease, which is often associated with osteoporosis because of malabsorption and poor nutrition; appropriate to measure a serum 25-hydroxyvitamin D at least once

24-hour urine testing: cost-effective; typically measure serum calcium and sodium simultaneously; in setting of normal renal function and adequate calcium intake, a 24-hour urinary calcium below 50 mg is highly suspicious for malabsorption; 24-hour calcium level above normal range may occur with primary hyperparathyroidism and hypercalcemia and commonly is seen with idiopathic hypercalciuria, which may increase risk of kidney stones and is sometimes treated with thiazide diuretic

Other laboratory tests that may be helpful in specific clinical circumstances: consider test of thyroid function in patient with suspected thyroid disorder or taking thyroid supplements; bone turnover markers such as C-terminal telopeptide (CTX), N-terminal telopeptide (NTX), and procollagen type 1 amino-terminal propeptide (P1NP) may provide helpful information; serum protein electrophoresis may be helpful in diagnosis of multiple myeloma; in patient with calcium disorder, measuring serum intact PTH may be helpful; if Cushing syndrome suspected, a test to evaluate cortisol, such as overnight dexamethasone suppression test is suggested; in rare cases, may be helpful to do double tetracycline transiliac bone biopsy

Management: NOF universal recommendations for osteoporosis management: encouragement of regular weight-bearing exercise, prevention of falls, avoiding tobacco and excess alcohol use, identifying and treating risk factors for fracture, encouraging vitamin D intake of 800 to 1000 IUs per day with a target of at least 30 ng/mL, and encouraging calcium intake of 1000 to 1200 mg/day, ideally from diet

Medication overview: all current medications for osteoporosis treatment reduce risk of vertebral fractures; this is requirement for approval; some medications are approved for prevention of postmenopausal osteoporosis; smaller number of drugs approved for prevention and treatment of glucocorticoid-induced osteoporosis; several drugs have been specifically tested and approved for treatment of osteoporosis in men

Medications for initial treatment of postmenopausal osteoporosis: two main groups, those that primarily inhibit bone absorption and those that primarily stimulate bone formation;

Bone-mineral absorption inhibitors: bisphosphonates; four now available in U.S., all as generics; these are alendronate (a weekly pill), risedronate and ibandronate (taken orally once per month) and zoledronic acid (an IV infusion, usually given once per year);

Bone-forming agents: teriparatide and abaloparatide; given as daily subcutaneous self-administered injections; limited to 24 months' maximum lifetime use, either individually or in combination, with drugs given at different times; important that they be followed by an anti-resorptive agent to enhance or maintain the benefit achieved with the bone-formation drug

Others: denosumab is a RANK ligand inhibitor; fully human monoclonal antibody administered as subcutaneous injection once every six months; raloxifene is a selective estrogen-receptor modulator; available generically; given as a daily pill; salmon calcitonin is a daily intranasal medication; various forms of estrogen are approved for osteoporosis prevention, including conjugated estrogen combined with bazedoxifene

Bone remodeling process (important for understanding of pathogenic process and mechanisms of action

of medications): remodeling initiated by activation event such as microfracture; large multinucleated cells called osteoclasts attach to bone surface; create acidic environment that dissolves bone mineral and express enzymes that degrade bone collagen; creates cavity; osteoblasts, more numerous, smaller cells, fill in cavity with osteoid, which is primarily a type 1 bone collagen, which subsequently becomes mineralized; if in balance, same amount of bone is replaced as is removed, and bone density remains stable; if not in balance, if more bone removed than replaced, then there is measurable loss of bone density, bone weakening, and increased fracture risk

- Medication side effects: with oral bisphosphonates, risk of GI upset, including upset stomach and heartburn; with IV bisphosphonates such as IV zoledronic acid, some patients experience acute phase reaction with transient flu-like symptoms, consisting of feverish feeling and achy bones and muscles; hypocalcemia may occur rarely after giving potent antiresorptive agent; renal toxicity has only been observed in IV bisphosphonates given quickly; therefore, IV zoledronic acid is recommended to be administered over at least 15 minutes; long-term side effects that have been associated with some osteoporosis medications, including bisphosphonates, include osteonecrosis of jaw and atypical femur fractures; possible side effects supported by no strong evidence include chronic musculoskeletal pain, atrial fibrillation, esophageal cancer, and impaired fracture healing
- Side benefits of long-term bisphosphonate therapy: may be prolonged joint-replacement survival; longevity of implants is likely to be better if osteoporosis is treated; improved mortality in patients being treated for osteoporosis
- Bisphosphonate holidays: American Society of Bone and Mineral Research has proposed consideration of temporary discontinuation of treatment with bisphosphonate in patients no longer at high risk for fracture; patients who have received oral bisphosphonate for at least five years or IV bisphosphonate for at least three years may be stratified according to level of fracture risk; if fracture risk is low, defined as hip T-score >-2.5 in a patient with no history of osteoporotic facture, consider drug holiday of two to three years; if fracture risk is high (T-score <−2.5), consider continuing oral bisphosphonate for up to 10 years and IV bisphosphonate for up to six years

Referral to osteoporosis specialist: American Association of Clinical Endocrinologists suggests referral if patient has normal bone density and low-trauma fracture; if patient being treated for osteoporosis has recurrent fractures or continued bone loss without obvious cause; if osteoporosis is unexpectedly severe or has unusual features; if patient has less common condition, such as hyperthyroidism or hyperparathyroidism; or if patient has condition (such as chronic renal disease or malabsorption) that complicates management

Reducing treatment gap: use of fracture liaison services in hospitals for secondary fracture prevention; treat-to-target concept, based on premise of doing more than having patient respond to treatment; want them to achieve acceptable level of fracture risk, as measured by, eg, improved T-score; new concepts for educating healthcare professionals, such as Bone Health TeleECHO, a videoconferencing technology using case-based learning to reach out to healthcare providers who could be located anywhere

Paget's Disease of Bone

Overview: though most clinicians rarely see this, studies suggest it is most common metabolic bone disease after osteoporosis, especially common in individuals of northern European descent; involves increased size and number of osteoclasts, localized area of excessive bone resorption and formation in one or more affected bones, with bone expansion, cortical thickening, lytic or sclerotic changes

Diagnosis: about 70% affected are asymptomatic; often recognized by lab or x-rays done for other reasons; laboratory test most often used to recognize it is serum alkaline phosphatase, a marker of bone formation; any level above normal, especially in absence of elevated liver enzymes, is suspicious; radiographs usually show characteristic appearances that can be confirmatory; good radiologist can recognize Paget's by x-rays in most cases; nuclear bone scan of whole body is often done to assess the extent; differential diagnosis of elevated bone-specific alkaline phosphatase includes metastatic cancer to bone, osteomalacia, hyperthyroidism, and hyperparathyroidism, as well as other conditions; goal of treatment is to relieve symptoms and prevent complications such as fractures

Treatment: indications for treatment are Paget's disease with total serum alkaline phosphatase at least two times upper limit of normal, having symptomatic Paget's (pain), or having risk of complications such as fractures; IV bisphosphonates are most common treatment; IV zoledronic acid most often used; zoledronic acid shown to be superior to risedronate; higher rate of alkaline phosphatase normalization than risedronate

Suggested Reading

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Reproductive Health

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Objectives: Review common disorders of reproductive health systems seen by general internist; discuss issues related to reproductive aging and hormone therapy

Case 1

A 22-year-old woman comes in with complaint of amenorrhea (I, irregular cycles) for 6 months; history includes regular menstrual cycles since undergoing menarche at age 12 yrs; at about age 18 yrs, started having more infrequent, irregular cycles; OBGYN placed her on birth control pills — regulated her cycles until age 20 yrs; stopped taking birth control pills, not liking side effects, and her cycles became progressively infrequent and irregular

Normal menstrual cycle: most women, during reproductive yrs, have regular menstrual cycles — typically ~28 days, but 25 to 35 days considered normal; at beginning of cycle, pituitary gland produces slightly increased levels of follicle-stimulating hormone (FSH) — stimulates follicle to begin to grow; follicle produces estrogen in increasing amounts as it grows and approaches time of ovulation; ovulation triggered by luteinizing hormone (LH) surge; during ovulation, egg released; then ovary produces progesterone and second peak of estrogen during luteal phase; when pregnancy doesn't occur, estradiol and progesterone levels fall, inducing menstruation, so body can reset and start another cycle

Ovulatory dysfunction: oligo-ovulation — cycles occurring at >35-day intervals; patient in case 1 clearly has oligo-ovulation; how to find cause of irregular cycles at 6 mos amenorrhea?

Differential diagnosis: for any woman of reproductive age with amenorrhea, consider pregnancy, easily assessed by urine pregnancy test or serum human chorionic gonadotropin (hCG) level — if positive, clear diagnosis; pregnancy test negative — differential diagnosis extensive; make diagnosis by breaking amenorrhea up into 2 separate categories: estrogenized anovulation or hypoestrogenic anovulation; *estrogenized anovulation:* polycystic ovarian syndrome (PCOS) most common cause: ovaries produce estrogen continuously along with excessive levels of androgens — also converted to estrogen; woman with PCOS has chronic estrogenized anovulation; different from woman with ovarian failure, premature menopause, or hypothalamic amenorrhea (*eg*, athletic amenorrhea or amenorrhea due to anorexia nervosa)

First step to determining cause of amenorrhea: determine estrogen status; several different ways to do; most often, progestin challenge test used but not good test, with this test, woman takes progesterone (often medroxyprogesterone acetate) for 5 to 10 days — any bleeding occurring thereafter considered estrogenized anovulation; not effective test for several reasons: almost half of hypoestrogenic women experience some degree of bleeding, so not good test for women with hypoestrogenic amenorrhea; 20% of women with chronic estrogen amenorrhea fail to bleed, so may be effective to induce bleeding or prevent dysfunctional bleeding; better diagnostic test for women with amenorrhea: ultrasound to look at endometrium and ovaries; endometrium of estrogenized woman — relatively thick (often >6 mm) but endometrium of hypoestrogenic woman — thin, usually no more than ~4 to ~6 mm; ultrasound also helps in second aspect of diagnosis: determining status of ovaries; few follicles and thin endometrium — pattern typical of ovarian failure; if many follicles and relatively thick endometrium — pattern typical of woman with PCOS; however, if thin endometrium and many follicles — ovaries have potential to function but are not — pattern of hypothalamic amenorrhea related to stress such as anorexia nervosa or what occurs with athletes

Amenorrhea: absence of menstruation for ≥6 mos; take careful medical history, performing good physical examination, pelvic examination, ultrasound, laboratory testing; when taking history, review conditions possibly associated with *stress-related amenorrhea:* weight loss, exercise, stress related to work or home life; patient typically has episodes of irregular cycles when under stress and more regular cycles when less stress; conditions including PCOS may be associated with estrogenized amenorrhea; other conditions that can cause estrogenized amenorrhea include thyroid dysfunction (especially hypothyroidism) and hyperprolactinemia; hyperprolactinemia and hyperthyroidism can also result in hypoestrogenic amenorrhea

Assessment: always include assessment of TSH, free T4, and prolactin in evaluation; for woman with primary amenorrhea, amenorrhea after giving birth, or amenorrhea after procedure such as dilatation and curettage (D&C), consider possibility of abnormalities of uterus, cervix, or vagina; *eg*, if woman had vigorous D&C, especially delayed after miscarriage, may have Asherman syndrome, or uterine adhesions; in woman with primary amenorrhea, if sexual development normal but only vaginal pouch and no vagina or uterus, may be Müllerian agenesis (*ie*, Mayer-Rokitansky-Küster-Hauser syndrome); if normal breast development but sparse pubic hair and exam reveals vaginal pouch but no

functional vagina, may indicate androgen insensitivity syndrome; important to consider all aspects and very important to include pelvic examination

Diagnostic testing: ultrasound — assess endometrium to determine if evidence of estrogen stimulation, as determined by endometrial thickness, and to assess ovaries; laboratory testing should include FSH, LH, TSH, free T4, prolactin; if diagnosis uncertain, blood level of anti-Müllerian hormone (AMH) — produced by small follicles in ovaries; woman transitioning to menopause has low AMH level; woman with PCOS typically has many follicles and high AMH level; FSH level important for assessing ovarian failure; women with ovarian failure and absent estrogen production have high FSH; important to consider that if follicle developing, estradiol level lowers FSH level; so, when measuring FSH, measure estradiol level to see if can interpret FSH; if estradiol level high, lowers FSH level and FSH level less meaningful; AMH minimally affected by other hormones, so it always gives accurate assessment of quantity of follicles in ovaries; AMH becoming more important, but *in terms of board examinations, FSH level critically important*

Treatment: woman with PCOS interested in managing symptoms can be prescribed birth control pills or other measures to lower estradiol and androgen levels; woman with PCOS trying to conceive should be successful with oral ovulation-induction agents; woman with hypothalamic amenorrhea — alleviation of causative stressors (nutritional, reducing exercise, or combination); woman with amenorrhea related to hyperprolactinemia — assess pituitary to ensure no prolactinoma or pituitary tumor; in most cases, treatment with dopamine agonist (*eg*, cabergoline or bromocriptine) can be effective in normalizing prolactin levels and restoring menstruation

For sake of argument, woman in case 1 has history of progressively irregular cycles, acne, oily skin, and hair growth on face, around nipples, and lower abdomen, but not in other locations

Hyperandrogenism syndrome: PCOS most common cause of hyperandrogenism; can result in hirsutism, irregular and infrequent cycles, acne, oily skin, and infertility; woman with PCOS has increased risk for depression; because of issues associated with hirsutism, hyperinsulinemia, and possibly central obesity, more likely to have body image problems

Differential diagnosis of hirsutism: goes beyond PCOS; includes familial hirsutism, Cushing syndrome, use of exogenous medications (especially androgen-containing medications); sometimes woman not aware medications or supplements contain androgens, so important to establish medical history and determine timing and onset of symptoms, especially in relation to menstrual history; rapid virilization resulting in temporal balding, male-pattern hair growth — concerning because of possibility of androgen-producing ovarian or adrenal tumor; in woman with rapid progression of hirsutism, assess for tumors;

Diagnostic testing: for woman with hirsutism and suspected PCOS, relatively straightforward — ultrasound of endometrium and ovaries and laboratory testing; labs overlaps some testing for amenorrhea; should include AMH, FSH, LH, estradiol, TSH, free T4, prolactin; in woman with hirsutism (especially rapidly progressive), assessment should include testosterone, dehydroepiandrosterone (DHEA) sulfate, and 17-hydroxyprogesterone; *testosterone:* elevated because of either exogenous hormones, or ovarian or adrenal production of testosterone; when woman has elevated testosterone, cannot know source of elevated testosterone without additional testing; in past, testosterone levels 2 times to 3 times upper limit of normal concerning for ovarian or adrenal tumor; imaging recommended; *DHEA sulfate:* primarily produced by adrenal gland; woman with elevated testosterone and DHEA sulfate probably hirsute because of adrenal source of androgen production; if testosterone elevated and DHEA sulfate normal, ovaries most likely source; *17-hydroxyprogesterone:* to assess for nonclassic congenital adrenal hyperplasia (also referred to as atypical congenital adrenal hyperplasia or late-onset adrenal hyperplasia); condition caused by enzymatic blockage of pathways in cortisol production; 21-hydroxylase deficiency more common; if deficiency allows some production of cortisol but not normal amounts, condition may go undetected at birth and only be determined when cycles irregular and woman presents with hirsutism as adult; important to measure 17-hydroxyprogesterone only before ovulation; level increases after ovulation along with progesterone levels; if 17-hydroxyprogesterone level and elevated and patient starts period within 2 weeks, level probably elevated because of ovulation — measurement should be repeated to determine whether or not truly elevated in early menstrual cycle

PCOS: diagnosis of exclusion

Diagnostic criteria: international congress established Rotterdam criteria; 2 out of 3 criteria, in absence of any other explanation, must be met for diagnosis; 1 — infrequent, irregular cycles (*eg*, cycles ≥35 days); 2 — signs or symptoms of excessive androgen: elevated levels of androgen, testosterone, DHEA sulfate; hyperadrenergic symptoms (*eg*, hirsutism, acne, oily skin); 3 — ultrasound appearance of ovaries consistent with PCOS (requires examination by vaginal ultrasound); 2 ways to meet ultrasound criteria: 1 — if ≥12 follicles in single plain in ovary; 2 — if ovarian volume ≥10 mL; however, if patient has ovarian cyst, cannot use volume calculation to determine whether or not she meets criteria for PCOS; volume used only in absence of ovarian cyst ≥1 cm

Other diagnostic considerations: many women with PCOS overweight or have insulin resistance, but diabetes or insulin resistance no longer considered diagnostic criterion for PCOS; AMH level tends to be elevated in women with PCOS, but not diagnostic criterion; LH:FSH ratio may be elevated, with relatively high LH compared with FSH, in women with PCOS, but also not diagnostic criterion; *diagnosis of PCOS requires exclusion of other causes of symptoms:* if woman has signs and symptoms of anorexia, eating disorder, or athletic amenorrhea, hypothalamic dysfunction primary diagnosis — she does not have PCOS, even if other criteria met; if patient has thyroid dysfunction or hyperprolactinemia, those would have to be corrected and signs and symptoms persist before PCOS diagnosis can be made; if patient has

21-hydroxylase deficiency, that would be primary diagnosis, not PCOS; same with Cushing syndrome; must consider all factors before establishing diagnosis

Treatment: help patient achieve personal goals; if hirsutism or hyperandrogenic symptoms, primary issue — control of hyperandrogenic symptoms; best way to accomplish — *combined oral contraceptives or combined hormonal contraception:* hormonal contraception decreases FSH and LH levels, causing ovarian stimulation to lessen — ovarian production of testosterone and estradiol diminishes; hair follicle growth occurs over long period of time — after ~6 mos of treatment, new hair follicles stop developing; existing terminal hair follicles that have converted from soft (vellus) follicles to coarse terminal hairs become somewhat softer; after ~6 mos, treatments such as *laser treatments or electrolysis* more effective than if initiated before contraceptives — before then, ongoing conversion of hair follicles and terminal hairs; treatment takes time to be effective — patients need to be encouraged that, with persistence, will eventually notice difference

Spironolactone: helps with hirsutism — reduces testosterone and limits effect of testosterone on receptors; in doses of 100 or 200 mg/d over 6 mos, combined with hormonal contraception, hair growth will decrease; unfortunately, no convincing studies in large patient groups that show spironolactone plus oral contraceptives more effective than oral contraceptives alone, but commonplace treatment and seems effective; *side effects of spironolactone:* hyperkalemia (avoid oversupplementation of potassium); spironolactone use without hormonal contraceptives discouraged; if woman using spironolactone and conceives and without realizing it (because cycles irregular) and continues to use it early in pregnancy, can cause feminization of male infant; spironolactone alone not considered primary treatment for hirsutism

Metformin and other agents: for women with PCOS interested in conceiving, metformin was increasingly used because theoretically corrects some underlying metabolic abnormalities associated with PCOS; however, prospective, multicenter, randomized, blinded study comparing clomiphene, metformin, and metformin plus clomiphene showed clomiphene superior to metformin in achieving pregnancies; also showed adding metformin to clomiphene did not significantly increase pregnancy rates; treat women with PCOS and diabetes with metformin — otherwise, role of metformin limited to treating women with diabetes, not to achieve pregnancy; follow-up study by NIH comparing clomiphene and letrozole (aromatase inhibitor) in women with PCOS showed letrozole, when used 5 days early on in cycle, causes drop in estradiol levels, which stimulates FSH to stimulate ovaries; more effective treatment than clomiphene; clomiphene and letrozole both considered category X (i*e*, contraindicated during pregnancy) — potentially cause birth defects, so pregnancy should be excluded each cycle before treatment initiated

Case 2

A 35-year-old woman reports unprotected intercourse with partner for 2 yrs and is still unable to conceive; concerned something may be wrong; has regular cycles every 28 days, 5 days of flow, and dysmenorrhea — completely alleviated with ibuprofen; asks what factors might contribute to her infertility

Infertility in women: mostly commonsense factors; if woman not ovulating, difficult to conceive; obstruction of fallopian tubes can cause infertility; misdirection of fallopian tubes can be caused by inflammatory conditions (*eg*, pelvic inflammatory disease [PID]) resulting in distal closure of fallopian tubes or distal tubal adhesions; if fallopian tube closes at distal end near ovaries, likely to cause hydrosalpinx and complete tubal occlusion — associated with sterility; requires advanced surgical treatment and likely in vitro fertilization (IVF); proximal tubal occlusion — can be caused by inflammatory conditions, often just false-positive result and diagnostic test (*ie*, hysterosalpingogram) should be ordered; abnormalities of uterus: congenital anomalies could have occurred during formation of uterus; woman with uterine agenesis or Müllerian agenesis not likely to conceive naturally; abnormalities in uterus shape resulting in formation of just 1 side of uterus (*eg*, unicorn uterus) typically not cause of infertility but increases risk for miscarriage; acquired abnormalities of uterus: uterine fibroids, endometrial polyps, and adhesions of uterine cavity referred (Asherman syndrome)

Evaluation and diagnostic testing: hysterosalpingogram (also allows for assessment of fallopian tubes); uterus can be assessed by saline infusions on hysterography (catheter placed into uterus, uterus filled with saline and distended to reveal polyp or adhesions in uterine cavity) or by hysteroscopy (camera placed directly into uterus); *cervical abnormalities:* can cause infertility but no good way to assess, aside from taking detailed history; *eg*, woman presenting with infertility has had aggressive cervical cone biopsy may have tubal infertility if cervical glands were removed during procedure; could also occur in women who underwent loop procedures of cervix for treatment after abnormal Pap smear; *conditions not often considered that may prevent intercourse:* infrequent intercourse because of pain or because of travel schedule; *detailed history:* should include factors potentially associated with infertility: history of PID, conditions that might cause endometriosis or manifest as endometriosis, assessment of uterine procedures, cervical procedures; *prior pregnancy history:* provides insight regarding female infertility; *semen analysis:* essential part of complete fertility evaluation, regardless of male's history of fertility — man's fertility can change as well as woman's; *assessment of peritoneal factors: eg*, endometriosis or pelvic adhesions — obtain from history; *ovarian reserve:* important, not at predicting ability to conceive, but in predicting ability to respond to fertility treatments, especially IVF; assess ovarian reserve by obtaining AMH level (most common), can be done at any point of cycle; basal FSH and estradiol provide insight if done early in cycle (usually day 3); assessing ovaries and number of small follicles via ultrasound, obtaining antral follicle count (*ie*, number of small follicles in both ovaries), provides information about ovarian reserve; woman with diminished ovarian reserve typically has low AMH and elevated FSH (≥10); low AMH defined as ≤1 ng/mL; antral follicle count shows <8 to 10 follicles, consistent with diminished ovarian

reserve; need to confirm by ultrasound; *ultrasound:* can give insight into various conditions (*eg*, endometriosis cysts in ovaries, other types of cysts in ovaries, presence or absence of hydrosalpinx, assessment of endometrium); standard part of infertility evaluation

Initiating infertility evaluation: have patient contact physician with start of her cycle; on day 3, obtain FSH, estradiol, and AMH levels, and perform ultrasound of uterus and ovaries; if history suggestive of hyper- or hypothyroidism, obtain thyroid function test; if cycles irregular, draw prolactin level along with thyroid function test; if evidence of hyperandrogenism, measure testosterone, DHEA sulfate, and 17-hydroxyprogesterone

Fertility treatment: most women successful with fertility treatment;

Menopause: diminished ovarian reserve early in menopause transition; women begin to have hot flashes, night sweats, sometimes up to 10 yrs before menopause; menopause defined as woman's last menstrual period; can only determine if woman has gone through menopause 1 yr later; during menopause transition, change in cycles; patients in late 30s or early 40s may complain that cycles closer together: loss of egg supply in ovaries or follicle depletion — occurs in early menopause transition; as follicles deplete, ovaries send weaker signal to hypothalamus and pituitary, so FSH levels increase; can occur even before onset of menstrual period; increased FSH levels cause growth of new follicles that get pushed to ovulate; if woman starts period and has follicle advanced in growth and development, not many days before she actually ovulates — rather than on day 14, may ovulate sooner (day 5-10); once woman ovulates, next period typically ~2 wks later; woman ovulating on day 14 usually has 28-day cycle, if ovulating on day 10, has 24-day cycle, if ovulating on day 6, has 20-day cycle; some patients may begin to experience vasomotor symptoms and shortening of cycles; as follicle depletion becomes more severe, elevated FSH levels cannot capture follicle — because no follicles; cycles start spacing out, becoming more irregular, less frequent; occurs in later menopause transition

Later in menopause transition: vasomotor symptoms typically increase and, if woman has irregular cycles, endometrial hyperplasia possible — sometimes requires endometrial biopsy, especially women aged >45 yrs with irregular cycles and abnormal bleeding over long time period; after menstrual periods cease, estradiol levels and estrogen levels are low; characteristic changes: vaginal atrophy (vaginal dryness usually develops over long period), emotional swings, sleep disorders (especially in patient who has night sweats); sleep disturbances can become severe, sometimes interfering with family and work life; usually peak within years of onset of menopause

Case 3

A 50-year-old woman presents with hot flashes; has tried OTC medications, including some advertised on TV; says they help a little for a while — maybe; reports severe hot flashes, night sweats, and sleep disorder, ruining her work life and home life; willing to try anything but fears breast cancer

Treatments: for most women, natural hormone therapy alternatives not effective; many prospective randomized studies, but studies often small and sponsored by hormone replacement therapy manufacturers; Franco et al 2016 study (*JAMA*) — meta-analysis of phytoestrogen efficacy, phytoestrogens, including soy, reduced hot flashes by only ~1 hot flash/day compared with placebo; placebo has powerful effect on vasomotor symptoms but does not last long; any study has to include placebo for comparison; in same paper, soy isoflavones specifically looked at, but only 0.8 hot flash/person/day — slight improvement in vaginal dryness scores, no change in vasomotor symptoms; American College of Obstetricians and Gynecologists (ACOG) position statement suggests no proven benefit of herbal remedies, but with soy and isoflavones, which contain phytoestrogens (plant estrogens), potential to cause problems in women with estrogen-dependent cancers; do not use in women, especially women with those cancers

Antidepressants: convincing evidence that selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI) antidepressants reduce hot flashes; for women with history of estrogen-dependent cancers, SSRIs and SNRIs best way to reduce vasomotor symptoms; in 2013, FDA approved paroxetine (SSRI) for modest to severe hot flashes based on 2 randomized trials in >1100 women; fewer hot flashes than placebo; common side effects — headaches, fatigue, nausea, vomiting; possibility that SSRIs may reduce tamoxifen efficacy; increased risk for bleeding and serotonin syndrome; for paroxetine and other SSRI antidepressants, all those treatments reduce hot flashes by 1 to 1.5/person/day compared with placebo; while effective, not as effective as desired;

Hormone therapy: many patients and providers fear hormone therapy — some based on evidence, some based on misunderstanding of data

Women's Health Initiative study: concluded that combined hormone therapy, when used in much older population, increased risk for invasive breast cancer, stroke, and venous thrombosis, but reduced colorectal cancer, hip fracture, and vertebral fracture; problem with study — age of population many years from menopause onset (*ie*, not population that would benefit from using hormone therapy, especially for symptom alleviation); newer studies and meta-analyses more reassuring; *long-term follow-up of Women's Health Initiative study:* 81% of women in study agreed to follow-up; only 4% continued hormone therapy; over time, risk in population was for breast cancer, but lower rates of endometrial cancer and hip fracture; breast soreness and vaginal bleeding obviously worsen with hormone therapy; urinary incontinence and gallbladder disease increased with combined hormone therapy; Women's Health Initiative showed no increase in risk for invasive breast cancer but increased risk for stroke, no significant reduction in colorectal cancer but reduction in hip and vertebral fractures; biggest concern in many women — breast cancer; in Women's Health Initiative study, breast cancer rates in older population treated was same for first 4 years, then diverged, with higher risk in combined therapy; good news — breast cancer declined remarkably after hormone therapy stopped; other studies have shown

relationship between hormone therapy, especially long-term, and breast cancer almost certainly real

Other studies: some studies have shown that hormone therapy, especially when initiated in older women, increases risk for dementia; however, joint tenderness and fractures significantly better, reduction in risk for diabetes; no difference in mortality, myocardial infarctions, cardiovascular deaths, incidence of other types of cancer (*eg*, lung and ovarian cancer), or deaths due to cancer (Mason, *JAMA* 2013); *open-label, randomized trial of combined hormone therapy vs placebo in >1000 recently postmenopausal women:* risk for death or hospital admission due to cardiovascular reasons much higher in placebo than in hormone therapy group (Sherbet, *BMJ* 2012); estrogen therapy for women who have had hysterectomy gives different results than combined therapy; *Nurses' Health Study (2012):* 121,700 nurses entered study at age 30 and 55 yrs in 1976; women who used hormone therapy for 10 to 15 yrs had 22% increased breast cancer risk, those who used estrogen or hormone therapy for 15 to 20 yrs had 43% increased risk; longer use associated with higher risk, but risk not appreciably increased in first decade after menopause

Bottom line: hormone therapy reduces menopause symptoms more dramatically than any other treatment; *learned over time:* lower doses also effective; prescribe lowest dose for shortest period to control symptoms; different formulations have comparable effects; no clear advantage to transdermal estrogen or transdermal estrogen-plus-progestin formulations compared with low-dose oral estrogens in terms of risk for thrombosis or other risks; *estrogen formulations:* pills, patches, sprays, gels, creams, vaginal rings, vaginal creams; *benefits of low-dose hormone therapy:* include marked relief of vasomotor symptoms but also relief of urogenital atrophy, reduced risk for osteoporosis; lower dose, lower risk for abnormal bleeding; *new combined hormone therapy:* FDA approved for women with vasomotor symptoms — contains combination of selective estrogen receptor modulator (bazedoxifene) combined with conjugated estrogen; reduces moderate to severe vasomotor symptoms including, hot flashes, and osteoporosis; antagonistic effect of bazedoxifene causes reduction of endometrial hyperplasia for 2 yrs; amenorrhea rates comparable to placebo; bazedoxifene also has protective effect on breast, does not appear to increase risk for breast cancer; downside — bazedoxifene plus conjugated estrogen associated with only 3 fewer hot flashes/day compared with placebo; bazedoxifene effective, can be used in women at high risk for endometrial or breast cancer with problematic vasomotor symptoms, but less effective than combined hormone therapy

Suggested Reading

Collins Fantasia H, Sutherland MA: Hormone therapy for the management of menopause symptoms. *J Obstet Gynecol Neonatal Nurs*. 2014;43(2):226-35; **Foster C, Al-Zubeidi H:** Menstrual irregularities. *Pediatr Ann*. 2018;47(1):e23-8; **Nandi A, Chen Z, Patel R, Poretsky L:** Polycystic ovary syndrome. *Endocrinol Metab Clin North Am*. 2014;43(1):123-47; **Sadow CA, Sahni VA:** Imaging female infertility. *Abdom Imaging*. 2014;39(1):92-107.

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Recurrent Urinary Tract Infections and Female Incontinence and Urgency

Erinn Myers, MD, *Assistant Professor of Obstetrics and Gynecology, Atrium Health, Charlotte, North Carolina*

Objectives: discuss recurrent urinary tract infections (UTIs), female incontinence, and urgency; common symptoms of urge and stress incontinence; approach to evaluation; treatment

Recurrent UTIs: defined as ≥2 infections in 6 mos or ≥3 in 1 yr

Risk factors: intercourse, specifically with a new sex partner within past yr; use of diaphragm or spermicide, even if spermicide-coated condoms; history of UTIs; diabetes; obesity; sickle cell trait; anatomic and congenital anomalies; stones, indwelling or repeat catheterizations; urinary incontinence; presence of cystocele; increased postvoid residual urine; vaginal atrophy

Treatment: first-line treatment — prevention; many interventions have not been adequately studied but many relatively safe, cause little to no harm, and worth trying — especially if minimize overall antibiotic use

Preventive measures: consider changing contraception type, attempt postcoital voiding, liberal fluid intake

Medical intervention: if prevention not effective; reasonable to empirically treat younger, uncomplicated, healthy patient with postcoital UTIs with postcoital prophylaxis without further evaluation; *eg*, trimethoprim (40 mg/200 mg), nitrofurantoin (50-100 mg), cephalexin (250 mg); if patient does not meet criteria for postcoital prophylaxis, other treatment strategies may include *continuous antibiotic prophylaxis:* nitrofurantoin (50-100 mg/d), trimethoprim/sulfamethoxazole (40 mg/200 mg 1×/d), trimethoprim alone (100 mg/d), cephalexin (125 mg/d); *topical estrogen:* can also be used in postmenopausal women; in 1 study, 0.5 mg estriol nightly for 2 weeks, then twice weekly for 8 months, significantly reduced UTI incidence compared with placebo: 0.5 episodes/patient-year vs 5.9 episodes/patient-year; increased estrogen increases prevalence of lactobacilli and decreases *E coli* vaginal colonization — helps minimize resistance in certain antibiotic treatments; *other treatments:* cranberry — efficacy not shown proven in studies to date; insufficient evidence for routine recommendation of probiotics; more research needed for methenamine salts and vaccines

Female incontinence and urgency: urinary incontinence present in 10% to 70% of women and up to 50% of nursing home residents

Risk factors: smoking (increases risk 2-3 times), obesity, menopause, pregnancy, age, childbirth, hysterectomy

Classifications of incontinence: stress urinary incontinence (leaking with coughing, running, jumping, sneezing); urgency urinary incontinence (overactive bladder spasms and leakage with urgency); mixed urinary incontinence (includes both stress and urgency); overflow, or hyposensitive bladder; leakage when reaching capacity; another type may include functional incontinence (not making it to bathroom on time because of physical or cognitive impairment or fistula); others

Patient evaluation: history and physical examination; laboratory tests, urodynamic testing, and voiding diary, if necessary; history of present illness can be extensive; important to ask about number of incontinence episodes per day or wk (baseline), number of pads per day, triggers (*eg*, coughing, running, jumping vs "I gotta go, I gotta go!"), frequency (>7-8 times/day), urgency, nocturia, enuresis, dysuria, hematuria, postvoid dribbling; also ask about volume lost — drops may indicate stress incontinence, flooding may indicate urgency incontinence; ask about voiding: hesitancy or difficulty with starting stream, sensation of incomplete bladder emptying, straining to empty; ask about history of incontinence procedures in past, medications; entire medical and social history

Physical examination, start with brief neurological examination, appreciating gait and perineal reflexes (*eg*, bulbocavernosus reflex, anal wink); next, inspect skin for vulvar and vaginal atrophy, excoriations, irritations, rashes; inspect urethra for discharge, diverticulum, masses, urethral caruncle, tender points; perform cough stress test and document if leakage; assess whether or not urethra mobile during cough test or perform Valsalva maneuver; inspect for fistula; with finger in vaginal area, ask patient to perform Kegel exercise to assess strength of levator muscles — possible need for physical therapy

Laboratory tests: important to rule out UTI as cause of leakage; urinalysis and culture may be indicated; if patient has recurrent UTIs, cystourethroscopy may be indicated to evaluate for mass, stone, or foreign body as source of recurrent UTI — especially if microscopic or gross hematuria in absence of UTI; postvoid residual helpful if concern about incomplete bladder emptying — assess with bladder scanner or in-and-out catheterization; bladder diary can be helpful to establish baseline symptoms and can be therapeutic for patient to understand drinking patterns and overall intake; instructions vary — usually, patient asked to keep 3-day diary of everything drunk; date, time, and volume recorded; ask patient to record every time she voids, including date, time, and volume; diaries

easily found online; patient needs to be given supplies for collecting and measuring urine; these activities also help rule out polyuria, polydipsia, and nocturnal polyuria; simple or complex urodynamic testing can be helpful for evaluating stress vs urgency incontinence; however, these tests typically reserved for patients with actual or suspected neurologic component (*eg*, trauma, Parkinson disease, multiple sclerosis); tests helpful for evaluating women contemplating surgical intervention; ultrasound and magnetic resonance imaging helpful if mass suspected

Treatment: treatment strategies differ based on type of incontinence; certain conservative therapies may improve symptoms for those with mixed urinary incontinence

Conservative therapies: lifestyle changes; *eg*, 8% weight loss can improve symptoms up to 50%; schedule or time voids to avoid urgency incontinence episodes; dietary modifications to avoid acidic foods, coffee, or carbonation; pelvic floor exercises; biofeedback; incontinence pessaries; for stress urinary incontinence alone, conservative therapies can be helpful; overactive bladder and urgency incontinence primarily treated medically once conservative therapies exhausted

Surgical intervention: surgical treatment such as midurethral sling and Burch urethropexy effective, with minimal risk

Medical management: usually begins with anticholinergic therapy; all medications have similar efficacy; treatment based on side-effect profile; side effects include dry mouth, dry eyes, constipation, cognitive dysfunction (rare); *medications:* oxybutynin, tolterodine, trospium, solifenacin, darifenacin, imipramine; beta-3 adrenergic receptor agonists also available — *eg*, mirabegron — stimulates relaxation of smooth muscle in bladder; *other options for urinary urgency:* cystoscopic injection of botulinum toxin into bladder and sacral neuromodulation; setting patient expectations important when managing urinary urgency — many treatment options decrease symptoms ~30% to ~50%; monitor and assess improvement, rather than cure; combining conservative and medical therapies can improve overall efficacy

Suggested Reading

Foxman B: Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am*. 2014;28(1):1-13; **Padmanabhan P, Dmochowski R:** Urinary incontinence in women: a comprehensive review of the pathophysiology, diagnosis and treatment. *Minerva Ginecol*. 2014;66(5):469-78; **Wood LN, Anger JT:** Urinary incontinence in women. *BMJ*. 2014;349:g4531.

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Testosterone Deficiency and Replacement

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Testosterone (T): male sex hormone; produced in testes by Leydig cells, with some testosterone production in the zona reticularis of the adrenal cortex; synthesized from cholesterol molecules through a multistep biochemical pathway; derangements in pathway cause reproducible syndromes of abnormal fetal and pubertal development; half-life of approximately 3 h; metabolized predominantly in the liver by conjugation or metabolism into 17-ketosteroids; metabolites excreted in bile, feces, and predominantly in urine; in peripheral tissues, testosterone undergoes conversion to dihydrotestosterone under the influence of 5-alpha reductase (5-AR) or aromatization into estradiol by aromatase; hormonal actions of downstream sex steroids play important physiological roles

- Circulating testosterone: found free, bound weakly to albumin, or bound tightly to sex hormone binding globulin; free and weakly bound fractions are bioavailable testosterone — often reported by laboratories, clinically significant in symptomatic patients; separate assays of free (unbound) testosterone and total testosterone levels often performed
- Production: peaks at several different points in development — during fetal period, drives normal gonadal differentiation; high levels persist until 6 months of age; testosterone peaks again at puberty, when male virilization occurs with development of secondary sex characteristics and sexual and reproductive capability; spermatogenesis, prostate growth, and production of seminal fluid begin or increase; testosterone production occurs in Leydig cells of testes under influence of circulating luteinizing hormone (LH); LH is produced in anterior pituitary and is under influence of pulsatile gonadotropin releasing hormone (GnRH) secretion by hypothalamus; both GnRH and LH production are limited by circulating testosterone levels in a negative feedback loop; testosterone replacement results in low levels of LH on laboratory assay and suppression of endogenous testosterone production
- Spermatogenesis: intratesticular testosterone diffuses into Sertoli cells and activates spermatogenesis; follicle stimulating hormone (FSH), made by the anterior pituitary, drives process as well; inhibin, produced by Sertoli cells as a marker of normal spermatogenesis, feeds back negatively on FSH production; the signaling loop comprised by these hormones is the HPG (hypothalamic-pituitary gonadal) axis; disruptions of the HPG are congenital, acquired, or due to disease processes or physical trauma; evaluation of FSH and LH levels, as well as other hormones produced by the pituitary, including prolactin and thyroid stimulating hormone (TSH), are important with abnormalities of testosterone production or spermatogenesis

Hypogonadism or low testosterone: defined by the Endocrine Society as two blood tests demonstrating total testosterone <350 ng/dL, or beneath the level defined by individual laboratory, and signs and symptoms consistent with hypogonadism; these include fatigue, decreased libido and sexual function, diminished exercise tolerance, decreased muscle mass, osteopenia, and change in cognition; many conditions can cause these complaints; thorough workup identifies other causes as well as secondary cause of hypogonadism, such as varicocele or pituitary disease

Testosterone Replacement

Off-label treatments: include clomiphene citrate, designed to stimulate endogenous testosterone production — assuming the patient has an intact HPG axis — and human chorionic gonadotropin (hCG) injections — assuming patient has normal testicular function; neither treatment suppresses spermatogenesis or endogenous testosterone production; no prospective, large-scale trial evaluating safety of clomiphene or hCG used for management of hypogonadism; retrospective uncontrolled cohort studies indicate treatments may be safe, but the patient should be reminded these are not FDA approved and safety is unknown

Safety of testosterone replacement therapy (TRT): controversial; numerous studies imply safety or risk from a cardiac or prostate health standpoint; there is no clear consensus as to whether heart or prostate health, as well as overall life expectancy, are impacted; monitoring should include a yearly digital rectal exam, quarterly blood tests — including testosterone levels, free and total, and a treatment peak, prostate-specific antigen testing (PSA), hemoglobin and hematocrit, and potentially annual hepatic function panel testing; counsel patients to anticipate suppressed sperm counts, testis shrinkage, some amount of polycythemia, some increase in PSA values, and some increase in benign prostatic enlargement and associated urinary symptoms; treat polycythemia with phlebotomy, and perform hematologic evaluation if hematocrit >53%; worsening urinary symptoms or persisting elevation in PSA value should prompt urologic evaluation; different forms of testosterone administration cause side effects to varying degrees; injectable testosterone causes greater polycythemia; obstructive sleep apnea, which can

predispose the patient to hypogonadism, can contribute to worsening polycythemia in the hypogonadal patient

Measurement: include peak measurements to ensure patient is not overreplaced; testosterone in short-acting or intermediate duration formulation requires specific instructions with regard to monitoring; gel applications require measurement of a testosterone peak level within 2-3 hours of gel application; measuring a level later results in a low measurement, as drug will have been cleared from the system; intermediate-length injectables, such as testosterone enanthate or testosterone cypionate, require a measurement within 2-4 days of injection to obtain accurate peak measurement; peak measurements are useful to confirm the patient is adequately replaced and not overreplaced; normal range should be 500-800 ng/dL; take peak measurements for either testopel or testosterone undecanoate 3 wks after administration; it may be as long as 6 months or more before symptomatic improvement is noted; symptom relief with testosterone replacement can be variable — commonly endorsed symptoms are often multifactorial; stabilization or reversal of signs of hypogonadism, such as osteopenia or truncal obesity, are demonstrable through bone scan or BMI measurement

Laboratory assays: measurements of total and free testosterone can be performed through immunoassay and radioimmunoassay, equilibrium dialysis, or liquid chromatography; no consensus as to the most accurate or cost-effective methodology; take measurements in the morning, given diurnal spike in testosterone production; complete evaluation of hypogonadism should include multiple morning testosterone measurements as well as gonadotropins, prolactin, sex hormone binding globulin, albumin, and TSH, in addition to a thorough physical exam; hormone panel provides global assessment of reproductive hormonal state; abnormalities of TSH or prolactin should prompt evaluation of the thyroid and pituitary, including imaging and endocrinological evaluation; varicocele, a varicose vein of the testis, obesity, and diabetes predispose to low testosterone; low testosterone more prevalent among opioid abusers and shift workers, who have disruption of circadian rhythm and suppression of morning testosterone peak

Transdermal formulations: most commonly prescribed in the US; include daily patch (Androderm), as well as transdermal gels in a 1.00% or 1.62% application (Testim, AndroGel, Fortesta and Axiron); generics are also available; gels require daily application; half-lives in the single digit hour range; daily administration is necessary for clinical effectiveness; absorption failure rate of 30% with no change in blood results despite appropriate daily application by patient, with equal failure rate of symptom relief; patch has significant associated skin irritation; gels carry risk of transfer to other people with whom the patient is physically intimate and require patient to be vigilant about covering application site or washing off the gel after an appropriate amount of time since application

Short-acting forms: Striant, a buccal testosterone product; Natesto, an intranasal spray; unique side effects of these products limit widespread usage — include gum irritation, rhinitis; Natesto requires multiple administrations per day, complicating compliance; preliminary data suggests Natesto has a unique effect of lack of suppression of pituitary gonadotropins

Long-acting forms: esterified injections — testosterone enanthate, decanoate, undecanoate, and cypionate; variable half-lives require re-dosing over course of weeks-months; testosterone undecanoate (Aveed) is longest acting with half-life of 70 days; Aveed has rare risk of oil micro embolism, requiring office administration or injection and observation after injection; alternate forms of testosterone injection do not require this; patients can be taught to self-inject safely; testopel, crystalline testosterone, is a second long-acting testosterone implanted into buttocks or abdominal wall fat in an in-office procedure performed every 3-6 months

Risk-benefit of Long-term Testosterone Replacement

Side effects: dependence on replacement and infertility are two unavoidable side effects; testicular hypofunction can cause problem with sperm counts; prior to initiating testosterone replacement, offer semen analysis to patients with interest in having children; there is a chance their baseline semen analysis will be abnormal; taking testosterone replacement suppresses activity of HPG axis; over time, chronic decrease in FSH and LH levels diminish function of Leydig and Sertoli cells in the testes with decreased sperm making and endogenous testosterone; eventually risk of these conditions becomes irreversible; some patients will stop testosterone replacement after years of treatment with a near normalization of their sperm count numbers or testosterone production; counsel all patients about these risks, because some patients will deal with these conditions on a permanent basis after stopping therapy

Benefits: improved bone density, muscle recovery and growth, and insulin sensitivity; aged patients are less likely to fall or fracture a bone; obese patients or type 2 diabetics may see an improvement in blood sugar control and weight loss efforts; benefits are more pronounced if the patient initiates a program of diet and exercise alongside testosterone replacement; various degrees of improvement in energy levels, concentration, sexual function, and libido; quality-of-life benefits are often strong motivators for patients to continue testosterone replacement

Cardiac Safety of Testosterone Replacement

Testosterone in older men (TOM) trial: randomized double-blind placebo-controlled trial of hypogonadal men >65 with limited mobility; improvements in physical activity were study endpoints

Methods: patients randomized to placebo or 1% testosterone gel with starting dose of 10 grams transdermally daily; dose titrated to level 500-1,000 ng/dL; study was halted by data and safety monitoring board due to adverse cardiovascular events, including acute coronary syndrome, myocardial infarction, stroke, and CHF exacerbation, plus one death due to suspected MI; in contrast, only one comparable event occurred in placebo group

Impact: discussion of cardiovascular risk inherent to testosterone replacement therapy came to the forefront; editorials in journals called for further research

Shortcomings: trial was not designed to determine risk of adverse cardiovascular events, nor was it powered to discern this effect; the statistical probability that its findings were simply due to chance is too high to accept its findings as scientifically valid; methodological factors,

including the testosterone replacement scheme — which used higher than standard replacement doses — and the population of patients studied — aged adults with some existing cardiac risk factors — may have influenced results; treatment and placebo groups were not balanced for cardiovascular risk factors such as hyperlipidemia

2010 Vigen retrospective cohort study: looked at testosterone administration and subsequent risk of adverse cardiovascular events, including heart attack or stroke; patients with documented low testosterone <300 ng/dL were considered; statistically significant difference in the hazard ratio regarding cardiovascular events was claimed; patients in the study — both those who received testosterone and those who did not — underwent a negative coronary angiography prior to initiating testosterone; transdermal gel was not considered; also concluded the absolute risk of cardiovascular event in a group of men with risk factors who received testosterone was relatively low

Shortcomings: although the cohorts in question — hypogonadal men with or without testosterone replacement — were followed for 3 yrs, there were no data available on treatment levels or adherence to treatment vs noncompliance; no standardization regarding method of administration of testosterone; patients receiving transdermal testosterone were far outweighed by patients on testosterone injections; statistical analysis used compared Kaplan-Meier curves of estimated event incidence; these indicated testosterone replacement was an independent risk factor for cardiovascular events; however, there was no need for an estimate with actual observed incidences available — raw data at 3 yrs of follow-up were available for both cohorts; those numbers translate to percentage differences suggesting testosterone replacement was actually protective; errors in methodology included overreporting of the number of patients excluded from analysis due to prior known myocardial infarction — this number had to be adjusted from 1132 patients to 128 patients, an error rate of almost 90%, as well a group of 100 women identified as having been included in the existing adverse cardiovascular events cohort by error; these errors resulted in calls for the paper to be withdrawn, though *JAMA* (*Journal of the American Medical Association*) has not mandated withdrawal

2013 Finkle retrospective cohort study: identified >55,000 patients given new prescription for testosterone replacement; group compared to >167,000 men given new prescription for phosphodiesterase type V inhibitors (Sildenafil or tadalafil); rates of nonfatal myocardial infarction within the 90-day post-prescription were considered; groups were compared to each other, and a comparison was made to the rate of MI in the 1 y prior to prescription administration; groups were divided between men >65 and all other men; the rate of nonfatal MI was calculated per 1,000 patient-y and the rate ratio reached statistical significance only in the group >65 y of age when compared to itself; both groups had increases in rate ratio that achieved statistical significance when compared with their age-matched cohorts receiving PDE5 inhibitor prescriptions; authors performed a number of covariate analyses to minimize the impact of comorbid conditions and concomitant medications; results retain statistical significance after these analyses

Shortcomings: no clinical data available for patients — including measurement of testosterone levels prior to or while on treatment, compliance, method of administration, and discontinuation rates; no discussion of the fact that patients obtaining a PDE5 inhibitor prescription were well risk-stratified prior to obtaining prescriptions; patients were screened regarding coexisting nitrate prescriptions such as nitroglycerin or isosorbide mononitrate (Imdur) or the presence of exertional angina and shortness of breath; PDE5 inhibitors cannot be prescribed to a patient with unstable angina without a cardiac workup, a patient with prior MI who requires Imdur, or a patient with stable angina whose symptoms resolve with nitroglycerin; excluding these patients may have altered results of the comparison; authors discuss these limitations openly in their conclusions

2016 Wallace retrospective cohort study: found increasing amounts of cumulative testosterone exposure conferred decreased risk of cardiovascular events, mortality, and risk of prostate cancer; all effects observed were highly statistically significant; cohort included 10,311 men >66 who received testosterone with a comparison cohort of >28,000 men age- and condition-matched; mean follow-up of patients observed within the study was >5 yrs; no additional risk of cardiovascular event identified in diabetics on testosterone replacement; overall risk of cardiovascular event for patients in both cohorts was 5%-6%

Shortcomings: inherent bias to retrospective studies, mortal time bias, and healthy patient bias; mortality increased in patients with the lowest but not zero exposure to testosterone; authors commented on difficulty determining causal relationships with any drug exposure in this sort of study and with this cohort of patients

Team trial: prospective, placebo-controlled trial of cognitive benefits of testosterone replacement in elderly males; enrollment and replacement protocols similar to the TOM trial; adverse cardiovascular event rate in the treatment group with 1-yr follow-up was negligible at 1%

2017 T trial: a randomized, double-blind study of men age ≥65 with levels and symptoms of low testosterone; found no difference in major adverse cardiovascular events between men randomized to testosterone replacement therapy and placebo; 7 men in each study group had major cardiovascular events during the treatment period; 2 men in the testosterone group and 9 men in the placebo group had major cardiovascular events during the subsequent year

2015 Sharma study: divided patients into 3 groups — testosterone replacement with normalization of levels, testosterone replacement without normalization of levels, and no normalization; testosterone replacement in hypogonadal men appeared to be cardioprotective with regard to risk of myocardial infarction or stroke, as well as all-cause mortality; mean follow-up was at least 4 y in all three groups; Sharma's group recently published a study in which testosterone replacement was also protective with regard to arrhythmia

Cheatham retrospective cohort study: strengths include close follow-up and centralized record system; men who received testosterone were less likely to develop MI or stroke or need coronary artery stenting; observed effect reached statistical significance; authors concluded testosterone replacement was protective with

regard to overall cardiovascular health; modality of testosterone administration, improvements in levels post-administration, and duration of therapy were reported

Low testosterone levels: associated with increased risk of metabolic syndrome and diabetes; Massachusetts Male Aging study found a 2-4-fold increase in risk of metabolic syndrome in men with a BMI <25 in the lowest quartile of total testosterone; testosterone deficiency is associated with cardiovascular risk factors — including increased carotid intima-media thickness, peripheral arterial disease, and elevated high-sensitivity C-reactive protein levels; testosterone deficiency is associated with an increase in both all-cause mortality and cardiovascular mortality

Metabolic syndrome and diabetes: several randomized controlled trials of testosterone therapy in men with testosterone deficiency showed improvement in components of metabolic syndrome, including dyslipidemia, insulin resistance, glycemic control, and inflammatory markers; meta-analysis of 20 studies show testosterone replacement is associated with both improved metabolic control and central obesity; whether improvement is a direct effect of testosterone therapy or the concurrent reduction in abdominal obesity is unknown; a longitudinal cohort study of men with type II diabetes found men with low testosterone levels had increased mortality rates; those who were treated had reduced mortality — suggesting testosterone replacement improved survival; although this was not a randomized trial, all patients were appropriately diagnosed, treated, and monitored per guideline recommendations

Cardiovascular mortality: large prospective cohort study found men in lowest quartile of total testosterone had increased mortality; another study also showed increased mortality and risk of both cardiovascular and respiratory disease among men in the lowest quartile of total testosterone; several subsequent studies and meta-analyses show association between testosterone deficiency and all-cause and cardiovascular mortality, including subpopulation with known coronary artery disease; some meta-analyses have shown only an increase in cardiovascular risk in elderly men with low testosterone levels — testosterone deficiency may simply be a marker of poor underlying health status; several studies found increased cardiovascular morbidity and mortality in men treated for prostate cancer with androgen deprivation therapy (ADT); it is unknown whether this increased risk is limited to those with pre-existing coronary artery disease; there is substantial data demonstrating adverse effects of ADT on traditional cardiovascular risk factors, such as serum lipoproteins, insulin sensitivity, and obesity

Cardiac benefits: randomized, controlled trials with testosterone therapy have shown improvement in functional capacity in men with coronary disease and chronic heart failure; a double-blind, randomized, placebo-controlled trial of men with stable angina treated with low-dose transdermal testosterone versus placebo showed a delay in time to 1 mm ST segment depression on treadmill exercise testing in the testosterone arm consistent with reduced exercise-induced myocardial ischemia; those with lower baseline testosterone levels had a greater magnitude of this response; another randomized placebo-controlled study showed improvement in myocardial ischemia with testosterone replacement therapy and a sustained effect to 12 months; a recent randomized placebo-controlled trial of men >60 with low to low normal testosterone levels showed no change in surrogate endpoints of carotid artery, intima-media thickness, and coronary artery calcium scores with use of testosterone gel vs placebo gel over 3 yrs

2017 Cardiovascular Trial: found a reduction in atherosclerosis among men treated with TRT; investigated effect of testosterone replacement on atherosclerotic plaque volume; followed patients for a year using CT coronary angiography; demonstrated increase in fibrous plaque in patients receiving testosterone with no major adverse cardiovascular events in either group; finding of a small absolute increase in fibrous plaque — as opposed to fatty or inflammatory plaque — carries unclear clinical significance; a prior cardiac trial used conversion of fatty plaque to fibrous plaque as a beneficial endpoint while studying effect of statins on plaque burden; underlying inflamed tissue within fatty plaque is what ruptures in MI, causing coronary artery obstruction; stabilizing fatty plaques is potentially beneficial; it is uncertain if this endpoint is clinically relevant to the patient's benefit or due to testosterone exposure

Limitations: whether a study was designed to investigate cardiovascular risk and specifics of the study design affect ability to widely apply any given study's findings to population; there are existing risk factors in hypogonadal patients with higher likelihoods of obesity, diabetes, hyperlipidemia, and coronary artery disease; there are known effects of testosterone replacement, including peripheral edema, fluid retention, and polycythemia; there are also unknown risks, such as the impact of aromatization of testosterone to estradiol

Counseling: evidence to date is inconclusive with regard to what effect, if any, testosterone replacement has on cardiovascular health; further prospective research is needed; close monitoring and behavior modification for cardiac risk — including smoking cessation, diet, exercise, and weight loss — can help mitigate any unknown existing risk; there is no basis for prohibition of testosterone replacement on hypogonadal men, even those with cardiac risk factors

Prostate

Prostate physiology: the prostate is a male reproductive organ of both endodermal and mesodermal origin; located in the pelvis, superior to the muscles of the pelvic floor and closely adjacent to the bladder neck and surrounding the posterior urethra; has glandular and muscular components that enable it to perform its unique function with ejaculation; prostatic secretions from the glandular component contribute to ejaculated seminal fluid; coordinated contractions of the muscular component along with the muscles of the pelvic floor and the bladder neck create antegrade ejaculation of seminal fluid; prostate is essentially important to reproductive function

Development: depends on actions of testosterone and its active metabolite dihydrotestosterone (DHT); these hormones enable the growth and proliferation of the glandular component of the prostate through activation of androgen receptors within the cytoplasm of prostatic epithelial cells; this proliferative growth is termed benign prostatic hyperplasia (BPH); lower urinary tract symptoms (LUTS) are associated symptoms in males

that arise because of this process; intracellular pathway enables carcinogenesis within prostatic epithelial cells, leading to prostate cancer; hypogonadism, BPH, and prostate cancer are all age-related conditions

Fetal Development: occurs at 10-12 weeks; prostate arises from urogenital sinus, which consists of an epithelial layer derived from endoderm surrounded by mesenchymal layer derived from mesoderm; invagination of epithelial folds and mesenchyme results in the glandular architecture of the prostate; proliferation of epithelial cells occurs under influence of testosterone; levels of testosterone in the male fetus are high; postpartum, elevation in testosterone peaks at 6 months, but can persist into the second year; testosterone is constantly converted by the intracellular enzyme 5-AR into DHT; 5-AR is found in high levels within cells of the prostatic epithelium as well as follicular cells of the scalp — DHT levels in part drive male pattern baldness; DHT is a more potent activator of androgen receptor than testosterone, binding to the receptor with a 10-fold greater affinity; in the male fetus, DHT drives organogenesis of both the male external genitalia and the prostate; as T levels fall after the second year of life, DHT levels fall correspondingly

Puberty: as the male child enters puberty, testosterone and DHT spike again, assuming an intact HPG axis; drives physical changes associated with sexual maturity and the onset of reproductive maturity; spermatogonial stem cells in the testes begin to undergo meiotic division into spermatozoa; in the prostate, proliferation of prostatic epithelial cells initiates prostate growth; prostatic secretion from these cells begins and the,patient begins to experience seminal emission, processes again driven by the influence of testosterone and DHT

Basis: much of what is understood about this process was observed in 5-AR-deficient patients who underwent a transition from phenotypic femaleness to maleness during puberty; in these patients, the massive spike in testosterone with puberty does not correspond to a spike in DHT, as there is no conversion of testosterone to DHT because of the absence of 5-AR; activation of the androgen receptor with increased levels of T alone is enough to drive the transition to phenotypic maleness and progression through puberty, increasing prostate size and size of external genitalia, development of pubic and axillary hair, as well as growth of muscle and bone — all occur to near normal degrees; difference in prostate in these patients is one of slower growth and decreased risk of prostate cancer throughout later life; this observation drove researchers to investigate 5-AR blockade as a pharmacologic mechanism for treatment of BPH and prostate cancer prevention

Benign prostatic hyperplasia (BPH): common problem affecting aging men; in 2000, there were 4.5 million physician visits related to BPH and 368 ambulatory surgery procedures performed per every 100,000 visits; relationship between BPH and associated LUTS is not entirely linear; although patients are more likely to develop LUTS as their prostate enlarges, it is not guaranteed; some patients with LUTS due to prostatic obstruction have small prostates; regardless, pharmacologic mechanisms for decreasing prostate size have long represented a high yield target for management of LUTS

Treatment: first commercially available 5-AR inhibitor was finasteride (trade name Proscar or Propecia); at a 5-mg daily dose, this drug is a first-line treatment for LUTS due to BPH; finasteride treatment results in a significant decrease in prostate size; when added to monotherapy for BPH with an alpha blocker, finasteride results in symptom improvement; dutasteride (trade name Avodart) is a second 5-AR inhibitor; dutasteride has some increase in efficacy attributable to its binding of all three isoforms of 5-AR within prostate epithelial cells, whereas finasteride binds only two; both drugs capitalize on the relationship between DHT and prostate growth first identified in 5-AR-deficient patients; blockade of 5-AR in prostate epithelial cells results in prevention of DHT production — this in turn removes a key driver of prostate growth; T levels in these patients remain unchanged — there is a small increase observed in T levels — and prostate size shrinks, confirming the theory that DHT is the key driver of BPH

Testosterone replacement and BPH: various formulations of testosterone all include warning language regarding worsening of urinary symptoms upon initiation of therapy; driving force behind this relationship is conversion of the supplemented testosterone into DHT, which drives BPH and worsening urinary symptoms in some, but not all, patients

Testosterone and prostate cancer: while castration can prevent advancement of metastatic prostate cancer, the relationship between testosterone levels and prostate carcinogenesis is unclear; two large, prospective, randomized, placebo-controlled trials examined the relationship between chronic 5-AR inhibitor usage and prostate cancer incidence — the REDUCE trial and the Prostate Cancer Prevention Trial (PCPT); both studies demonstrated a 30% risk reduction in development of prostate cancer over a 10-yr window; some concern regarding slight increases in high-risk cancers in treatment arms of both studies was dismissed as due to detection bias as opposed to treatment effect; concluded DHT levels can in part drive prostate carcinogenesis and decreasing these levels, in addition to preventing prostate enlargement, can prevent prostate cancer; corresponding question of whether T levels themselves influence prostate cancer risk remains unanswered; numerous data point to different conclusions; some studies implicate low testosterone levels in conferring a higher likelihood of prostate cancer, implying more than one pathway for prostate carcinogenesis might exist; although low testosterone levels should correlate to low DHT levels — suggesting hypogonadal patients would be less likely to develop prostate cancer — the common observation that both prostate cancer and low T are diseases of aging men confounds the picture; a man in his 80s is far more likely to have both low testosterone and prostate cancer than he was in his 20s; whether or not this observation is correlative but not causal remains to be proved; further study is warranted

Suggested Reading

Corona G et al: Testosterone Replacement Therapy: Long-Term Safety and Efficacy. *World J Mens Health* 2017 Aug;35(2):65-76; **Elliott J et al:** Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis. *BMJ Open* 2017 Nov;7(11); **Goodale T et al:** Testosterone and the Heart. *Methodist Debakey Cardiovasc J* 2017 Jun;13(2):68-72.

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The General Approach to the Treatment and Prevention of Infections

Marisa Holubar, MD, *Clinical Assistant Professor of Infectious Diseases, Associate Director of Antimicrobial Stewardship and Infection Control Programs, Stanford Medical School*

Infections: frontline clinicians are critical to antimicrobial stewardship efforts; antimicrobial stewardship is defined as coordinated interventions designed to promote the optimal use of antibiotic agents, including their choice, dosing, route, and duration of administration; half of all hospitalized patients receive an antibiotic and 30-50% are inappropriate; antibiotics are also commonly prescribed in the outpatient setting; the CDC estimates that 30% of all antibiotics prescribed in outpatient clinics are unnecessary; when antibiotics are indicated, prescribers often favor drugs that may be less effective or carry more risk over targeted first-line drugs recommended by national guidelines; internists prescribed 30 million antibiotics in 2014

- Negative outcomes associated with antibiotics: antimicrobial resistance — bacteria develop resistance to antibiotics upon exposure; this is inevitable and unique to antimicrobials; unlike any other class of drugs, the use of antibiotics creates selective pressure that allows for the emergence of resistance; for this reason, antibiotics have built-in obsolescence; because of this, each use of antibiotics has a potential public health consequence; for individual patients, exposure to antibiotics may result in an allergic reaction, end-organ damage (including nephrological or hepatic toxicity), drug-drug interactions (common issue for many antibiotics), cost, and an impact on the human microbiome; antibiotics decimate the normal flora of the gut; gut dysbiosis is linked to *C. difficile* colitis and has also been linked to other adverse health outcomes (eg, decreased response to chemotherapeutic agents); antibiotic use has also been linked to colonization with resistant bacteria, which may complicate future treatment for other common infections
- American Board of Internal Medicine high-value care statement: "Suboptimal use of antimicrobial agents drives the emergence of antimicrobial resistance, leads to poor outcomes, and increases adverse events and cost;" antimicrobial stewardship is good clinical practice; the principles of antimicrobial use are in line with antimicrobial stewardship principles
- Categories of antimicrobial use: used prophylactically to prevent infection, eg, prior to surgery to prevent surgical site infections, to prevent opportunistic infections in immunocompromised patients, as with the use of trimethoprim sulfamethoxazole to prevent pneumocystis infections in patients receiving chronic steroids; used empirically when infection is suspected, but before microbiologic data are available to support a specific diagnosis (most antibiotic use in both the inpatient and outpatient setting); therapy is considered definitive or targeted when it is specifically directed at a pathogen that has grown on microbiologic studies, which often include susceptibility testing; used preemptively to abort infection; the commonest use of preemptive therapy occurs in immunosuppressed transplant recipients who receive antivirals to prevent the development of end-organ infections with cytomegalovirus circulating in their blood
- Empiric microbials: prescribed to patients with suspected infection; choice of regimen depends on the suspected source of infection and the clinical and immune status of the patient; clinicians must recognize and consider the risk of infection due to a drug-resistant organism; one of the greatest risk factors for developing an infection due to a drug-resistant organism is the receipt of antimicrobials for any indication within the last 3-6 months; in most cases, empiric regimens are considered broad spectrum because the infecting organism is unknown; particularly true in infections in hospitalized patients, including those presenting with sepsis or healthcare-associated pneumonia; tailoring antimicrobial therapy is key for clinical management
- High-value care statement: "Empiric antimicrobial therapy should be modified or deescalated as soon as culture results become available to provide the narrowest spectrum agent available;" an accurate diagnosis is critical; we must appropriately use the microbiology lab; culture results should be obtained when the index of suspicion is high and through sterile technique to avoid detecting organisms that are not clinically relevant (eg, those colonizing in-dwelling devices, organisms colonizing the patient's skin)

- Culture technique pearls: cultures should be obtained prior to starting antibiotics; pretreatment with antibiotics reduces the yield of blood cultures by as much as one-third; blood cultures should be obtained in appropriate volume to optimize sensitivity; draw blood cultures from at least 2 separate sites to distinguish actual pathogens from contaminants and to identify real infections caused by organisms which are frequently contaminants; do not draw cultures through indwelling catheters — high risk of contamination; urine cultures should only be obtained if patient is symptomatic; use clean-catch technique; do not treat asymptomatic bacteriuria; do not obtain cultures unless infection is suspected
- Antibiotic reevaluation: reevaluate daily antibiotics prescribed in the hospital; reevaluate antibiotic therapy at 48-72 hours after empiric therapy initiation, because

microbiologic data are often available; the patient's clinical evolution can be taken into account; narrower-spectrum, more appropriate antibiotic can be prescribed; the CDC refers to this as an antibiotic timeout; during reevaluation, clinicians can reassess the antibiotic route of administration (eg, intravenous [IV] to oral switch); empiric IV antibiotics are often indicated when a patient is admitted, but many patients can complete their course with targeted oral antibiotics after they begin to improve; switching to oral antibiotics can decrease cost, facilitate discharge, and save patients from complications associated with in-dwelling intravenous catheters such as infection and clots; some life-threatening infections are not eligible for an IV to oral antibiotic switch (eg, meningitis, endocarditis); many commonly encountered infections are eligible (eg, community-acquired pneumonia, urinary tract infections [UTIs], skin and soft tissue infections); a patient is eligible for an IV to oral conversion of antibiotics if you can answer yes to 4 questions; 1) is the patient improving clinically and is she hemodynamically stable? 2) is the patient tolerating food or enteral feeding? note that effectiveness of some antibiotics, eg, fluoroquinolones, is reduced with enteral tube feeding; feeds can be held 1 hour before and after drug administration; 3) is the patient able to adequately absorb orally administered medications (ie, is the patient taking other important medications, such as cardiac medications, orally)? patients with persistent nausea and vomiting, active gastrointestinal bleed, ileus malabsorption syndromes, or proximal resection of their small intestines may not be candidates for orally administered antibiotics; 4) is there an orally bioavailable antibiotic that would adequately treat the infection? bioavailable oral antibiotics achieve serum and tissue concentrations that are comparable to IV-administered antibiotics

Bioavailable oral antibiotics: fluoroquinolones, doxycycline, azithromycin, trimethoprim-sulfamethoxazole, metronidazole, fluconazole, and cephalexin; linezolid and tedizolid have excellent oral bioavailability, but use should be reserved for situations in which alternative options are not available; other antibiotics with adequate oral bioavailability include amoxicillin, amoxicillin clavulanate, and cefpodoxime; in many hospitals, protocols allow pharmacists to automatically interchange IV formulations with orally bioavailable formulations of the same drug if patients are clinically stable, able to absorb orally administered medications, and are tolerating oral drugs or diets

High-value care statements: 1) "In patients taking intravenous antimicrobial therapy, a switch to oral therapy should be considered in all patients with an intact and functioning gastrointestinal tract and whose clinical status is improving;" 2)"continued in-hospital monitoring of stable patients following the transition from parenteral to oral therapy has not been shown to improve outcomes, at least in pneumonia"

Duration of antibiotics: durations of antibiotics for common infections are generally not based on robust clinical evidence, but on expert opinion or what clinician learned in training

Community-acquired pneumonia: international guidelines have supported short-course therapy for many years; the 2007 Infectious Disease Society of America (ISDA) and American Thoracic Society guidelines recommended that patients with community-acquired pneumonia be treated for a minimum of 5 days; antibiotics should be continued until patients are afebrile for at least 48 hours and are clinically improved before discontinuation; guidelines validated in recent, randomized clinical trial

Complicated intra-abdominal infections: the 2010 IDSA and Surgical Infection Society guidelines for the management of complicated intra-abdominal infections recommended that antimicrobial therapy be limited to 4-7 days unless adequate source control was not possible; STOP-IT trial validated 4-day course in patients in whom source control was obtained; some evidence suggests that we can treat bacteremias due to Gram-negative rods, especially those complicating UTIs, with 7 vs 14 days of therapy

Antibiotic update: as antimicrobial resistance has emerged as a global public health threat, fewer new antibiotics are on the market; referred to as the "diminishing antibiotic pipeline," a major issue when we talk about future infection management; only 15 new antibiotics have been approved since 2000, with few novel mechanisms of action

Trimethoprim-sulfamethoxazole (ie, cotrimoxazole, TMP-SMX): a combination of two agents that act synergistically to prevent formation of tetrahydrofolic acid, ultimately inhibiting thymidine synthesis and subsequently bacterial DNA synthesis; uses include skin and soft tissue infections, primarily those due to methicillin-resistant *Staphylococcus aureus* (MRSA); highly orally bioavailable with excellent tissue penetration; despite the emergence of resistance among *S. aureus* strains in the community, has retained activity against MRSA; should be primarily used for purulent cellulitis, commonly caused by *S. aureus*; though effectiveness of TMP-SMX against *Streptococcus* has been questioned, a randomized controlled trial of outpatients with skin and soft tissue infections likely due to *Streptococcus* showed no difference in clinical cure between those that were treated with clindamycin and those treated with TMP-SMX; adding a second agent to TMP-SMX for *Streptococcus* coverage is unnecessary; trial shows both clindamycin and TMP-SMX are effective against *S. aureus*, including MRSA; TMP-SMX is a first-line agent for infections secondary to *Stenotrophomonas* or *Pneumocystis*, and *Nocardia* species; common side effects are gastrointestinal disturbance and rash; has also been associated with renal injury and electrolyte disturbance (especially hyperkalemia); use is complicated by many drug-drug interactions; it is associated with some life-threatening adverse effects, including uncommon severe dermatologic reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis)

Polymyxins: (eg, colistin or polymyxin B) have been used with increasing frequency, but use should be reserved for infections due to drug-resistant, Gram-negative organisms (eg, *Acinetobacter*, carbapenem-resistant *Enterobacteriaceae*, drug-resistant *Pseudomonas*) because these drugs are associated with significant adverse events; polymyxin B is favored at some facilities because of its more favorable pharmacokinetic properties; polymyxin B is an active drug whereas

colistin is administered as a prodrug and has variable and slow conversion to its active moiety; polymyxin B may be less nephrotoxic, although it is also associated with some neurotoxicity; polymyxin B does not penetrate the bladder and should not be used for treating UTIs secondary to these drug-resistant organisms

Aminoglycosides: resurgence of use in certain circumstances, including when used in combination to treat infections due to drug-resistant, Gram-negative infections; bind to 16S ribosomal RNA and disrupt bacterial peptide elongation; all have a similar spectrum of activity targeting aerobic Gram-negative pathogens; synergistic in treating infections due to *Streptococcus* or *Enterococcus*, but should not be used alone to treat infections due to Gram-positive infections; are used against some mycobacterial infections; activity against bacteria is concentration dependent; goal is to maximize drug concentration at the site of infection; administered via high-dose, extended interval therapy for most situations; interval at which these drugs are administered depends on a patient's renal function because they are renally cleared; associated adverse events are nephro- and ototoxicity; lassomycin is a new aminoglycoside coming to market; approved for use in complicated UTIs and bloodstream infections; appears to be more potent than other aminoglycosides; appears to have retained activity against many *Enterobacteriaceae* that are resistant to other aminoglycosides (eg, tobramycin or gentamicin)

Rifamycins: most commonly used is rifampin; used primarily for mycobacterial infections and as an adjunct for deep-seated staphylococcal infections, especially those associated with prosthetic material (eg, prosthetic joint infections, prosthetic valve endocarditis); rate of resistance development is high; never used as monotherapy except when used (rarely) as prophylaxis against *Neisseria meningitidis* or *Haemophilus influenzae*; moderate to potent inducers of drugs undergoing metabolism by cytochrome p450 enzyme system; be aware of many drug-drug interactions

New antibiotics: several have been released on the market over the last several years; most target Gram-positive organisms and include MRSA in their spectrum of action

Daptomycin: a lipopeptide antibiotic; a large molecule that inserts itself into a bacterial cell membrane in a calcium-dependent manner, disrupting cell membrane integrity and function; has activity against Gram-positive organisms, including MRSA and vancomycin-resistant *Enterococcus* (VRE); primarily used for deep-seated infections (eg, bacteremia, bone and joint infections); inactivated by pulmonary surfactant in the lungs, so cannot be used to treat pneumonia; associated with rhabdomyolysis, which is diagnosed when creatine kinase is >5 times the upper limit of normal; follow patient's creatine kinase during prolonged use

Lipoglycopeptides: telavancin, oritavancin, and dalbavancin; interfere with cell wall synthesis and are active against Gram-positive agents, namely MRSA and *Enterococcus*; dalbavancin and oritavancin also have activity against VRE; all approved for treating complicated skin and skin structure infections; telavancin has been associated with increased mortality in patients with renal insufficiency, so should be avoided in these populations; oritavancin and dalbavancin have extremely long half-lives and do not require daily administration; most appropriate use is a subject of debate; used as salvage therapy for complicated infections (eg, relapsed MRSA bloodstream infections)

Oxazolidinones: linezolid and tedizolid; inhibit bacterial protein synthesis by binding to the 23 ribosomal RNA of the 50S ribosomal subunit, preventing the formation of the 70S initiation complex; activity against Gram-positive organisms, including MRSA and VRE; linezolid is available in PO and IV formulations; excellent oral bioavailability; linezolid is FDA approved for the treatment of pneumonia and skin and soft tissue infections, but has been used in off-label indications (eg, consideration for salvage therapy for relapsed *S. aureus* bacteremia); toxicities include peripheral and optic neuropathy and myelosuppression, especially with long-term use; linezolid is a weak monoamine oxidase inhibitor, so it can precipitate serotonin toxicity when co-administered with certain drugs (eg, selective serotonin reuptake inhibitors [SSRIs], bupropion); tedizolid has key structural differences that allow additional target binding site interactions; accounts for greater potency and retained activity despite linezolid resistance; it is thought to cause less myelosuppression than linezolid; although it is a reversible inhibitor of monoamine oxidase *in vitro*, drug-drug interactions with SSRIs and others have not been evaluated in clinical trials

New beta-lactams: ceftaroline is considered a fifth-generation cephalosporin; activity includes Gram-negative coverage comparable to ceftriaxone; primarily Gram-positive coverage, which includes MRSA and some cases of VRE; holes in coverage include nosocomial Gram-negative organisms (eg, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*); FDA approved for use in patients with community-acquired pneumonia or skin and soft tissue infections; like linezolid, use in a variety of other invasive infections (eg, MRSA bacteremia) has increased; generally well tolerated; neutropenia reported in up to 10% of patients; like many other new drugs, it is expensive

Beta-lactam/beta-lactamase inhibitor combinations: ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem/vaborbactam; beta-lactamase inhibitors have very little intrinsic antibacterial activity, but they inhibit the activity of a number of plasmid-mediated beta-lactamases; the addition of avibactam and vaborbactam, which are new beta-lactamase inhibitors, provides activity against some but not all carbapenemases; ceftolozane/tazobactam includes ceftolozane (a novel cephalosporin, which has limited Gram-positive activity); in clinical trials, it has performed well vs fluoroquinolones for complicated UTIs and vs meropenem for complicated intra-abdominal infections; does not include anaerobes in spectrum of activity, so must be administered with metronidazole; primary activity against multi-drug resistant *Pseudomonas*; many believe use should be reserved for patients with pseudomonal infections secondary to carbapenem-resistant *Pseudomonas*; ceftazidime/avibactam has activity against most

Enterobacteriaceae, including those that produce AmpC beta-lactamase, extended spectrum beta-lactamase, some carbapenemases, and multi-drug resistant *Pseudomonas*; meropenem/vaborbactam has a similar spectrum of activity as ceftazidime/avibactam, but does not include enhanced clinical activity against carbapenem-resistant *Pseudomonas aeruginosa* or *Acinetobacter*; both ceftazidime/avibactam and meropenem/vaborbactam have activity against *Klebsiella pneumoniae* carbapenemases, or KPC-producing *Enterobacteriaceae*; KPC is the most common carbapenemase that we see in the US; none of these new drugs inhibit second-most-common carbapenemase seen on a worldwide scale, which is the New Delhi metallo-beta-lactamase or NDM carbapenemase; all demonstrate time-dependent killing (in contrast to aminoglycosides, whose activity is concentration dependent); for beta-lactamases, important to optimize the duration of time that the pathogen is exposed; the prolonged infusion of beta-lactams over 4 hours at each dose, or continuously, has gained popularity, especially for patients that are critically ill, have renal compromise or fluctuating renal status, and patients that are infected with less-susceptible pathogens; many facilities have defaulted to the extended infusion protocols to optimize use of beta-lactams

- Tigecycline: very broad-spectrum activity against Gram positives (eg, MRSA and VRE), Gram-negatives, and anaerobes; does not attain high serum concentration so cannot be used for bacteremia; does not attain good urine concentrations so cannot be used for UTIs; in 2013, the FDA added a black box warning to this drug due to an increased risk of death observed in patients receiving the drug in clinical trials

Limiting transmission of infections: incredibly important to stewardship efforts because we do not have to use antibiotics if patients avoid infections; reinforce the importance of hygiene in prevention of transmission of infection; the most important thing you can do as a healthcare provider to limit the transmission of infection

- High-value care statement: "Limiting transmission is best accomplished by full compliance with hand hygiene protocols for both healthcare workers and patients"
- Vaccination: another way to limit transmission; in the US, the Advisory Committee of Immunization Practices (ACIP) of the CDC provides recommendations for vaccinations for all age groups; despite very successful pediatric immunization programs in the US, administration rates for adults aged ≥65 are much lower; the CDC reports that immunization rates against influenza and *Pneumococcus* in at-risk young adults remains unacceptably low
  - Influenza vaccination: annual vaccination is a critical public health measure against this highly infectious microorganism; generally offered at the end of October, but should be actively vaccinating individuals through the end of flu season; virus is remarkable for its high rate of mutation; new vaccines are produced each year to best match circulating strains; in some years, there are mismatches between the vaccine strains and the circulating strain that results in reduced vaccine efficacy; immunity is not long lasting; annual immunization is necessary because of mutations that develop and waning immunity; two types of vaccines are available in the US — inactivated influenza vaccine and a live-attenuated vaccine; the live-attenuated vaccine is approved for healthy, non-pregnant individuals who are between the ages of 2 and 49; there is also a formulation considered to be a high-dose, inactivated influenza vaccine, which is recommended for individuals >65 years of age because it is more immunogenic and effective than standard-dose vaccine; has also been shown to be cost effective; ACIP recommends annual vaccination for all persons aged 6 months or older who do not have contraindications; ACIP recommends that in shortage situations, we focus on delivering the vaccine to high-risk groups — children, adults older than 50 years of age, those with chronic conditions (eg, cardiac, pulmonary diseases), those with diabetes mellitus, immunocompromised individuals (eg, those with HIV), women who are pregnant or trying to become pregnant, those with extreme obesity (ie, body mass index ≥40), residents of long-term facilities, or caregivers or contacts of those at risk (eg, healthcare providers)
  - Pneumococcal vaccination: >90 different pneumococcal serotypes that circulate; vaccines target serotypes most commonly associated with invasive disease; vaccines induce antibodies to the polysaccharides on the capsule of the bacteria, which is one of its greatest virulence factors; two types of vaccines licensed in the US — pneumococcal polysaccharide vaccine and pneumococcal conjugate vaccine; the pneumococcal polysaccharide vaccine is older; it contains capsular polysaccharides for 23 common infecting serotypes; recommended for adults older than 65 and for younger adults at risk of developing pneumococcal disease (eg, patients with functional or anatomic asplenia, immunocompromised individuals, patients with a cerebral spinal fluid leak, patients with advanced kidney disease, or those that have cochlear implants); pneumococcal conjugate vaccine targets 7 serotypes that are most commonly associated with pneumococcal disease in young children; in this formulation, polysaccharides are covalently linked to a conjugate, which is a non-toxic protein that is nearly identical to the diphtheria toxin; this renders the vaccine more immunogenic in infants and toddlers; in 2012, ACIP recommended the sequential administration of these two vaccines for adults >18 years of age who are at risk of serious pneumococcal infection; in 2014, extended recommendation to all adults >65 years of age; if a patient has not received either, ACIP recommends to start with the pneumococcal conjugate vaccine followed by the polysaccharide vaccine at least 8 weeks later; re-vaccination intervals for subsequent doses of the pneumococcal polysaccharide vaccine vary with age and immune status; re-vaccination with the pneumococcal conjugate vaccine is not recommended
  - Varicella zoster vaccine: *Varicella zoster* virus causes a primary infection (chicken pox), but also can cause herpes zoster (shingles), which is due to the reactivation of latent virus in neurons within sensory ganglia; cell-mediated immunity, which limits this reactivation, wanes with advanced

age, and is also compromised in patients that are immunosuppressed; two types of vaccines are licensed in the US — non-live recombinant glycoprotein E vaccine and a live-attenuated vaccine; in 2017, ACIP recommended preference of the recombinant vaccine due to higher rates of efficacy against herpes zoster and more long-lasting protection; vaccination is recommended for all individuals older than age 50; it is not necessary to determine if patients have a history of varicella or zoster prior to vaccination; vaccination is recommended for patients taking low-dose immunosuppressive medications, those anticipating immunosuppression, or have recently recovered from immunosuppression; ACIP has not made recommendations for this vaccine for other immunocompromised hosts or those receiving high-dose immunosuppression because there are no supportive clinical data

Hepatitis B: vaccination against hepatitis B is a very important public health measure; 5-10% of individuals will not respond to currently available vaccines; ACIP recommends vaccination of high-risk adults (eg, those at risk for infection by sexual exposure, those with a history of current or recent injection drug use, those at risk for percutaneous or mucosal blood exposure [healthcare workers, first responders, patients undergoing dialysis], travelers to hepatitis B-endemic countries, patients with hepatitis C infection and chronic liver disease, and patients with chronic liver disease [transaminases greater than 2 times the upper limit of normal]); vaccinate non-immune pregnant women at risk of becoming infected with hepatitis B during their pregnancy; available vaccinations include a combination hepatitis B and hepatitis A vaccine; all formulations are administered in a series; a new vaccine (hep B CPG) appears to be more immunogenic, but optimal use has yet to be determined due to safety concerns

Fever of unknown origin (FUO): refers to a prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing; classically, FUOs were defined as illnesses that lasted ≥3 weeks in a patient with a temperature greater than 38.3°C or 101°F on several occasions, and whose diagnosis remained uncertain despite evaluation in the hospital for ≥1 week; definition derived from studies performed in the 1960s; there have been many proposed refinements to this definition, including eliminating the in-hospital component because of increased sophistication of outpatient evaluation and taking into account the immune status of the individual, which changes the differential diagnosis; 3 general categories of illnesses account for the majority of classic FUO cases — infections, malignancies, and systemic rheumatologic or inflammatory diseases; each category frequency differs geographically; over time, proportion of cases caused by these categories also changed within specific geographies; infections account for fewer cases of FUO now, in part because of improved diagnostics; in the past, subacute endocarditis was a common cause of FUO because it was challenging to identify some organisms in culture, including the HACEK organisms (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis, Eikinella corrodens, Kingella* species); present-day blood culture systems are capable of detecting these organisms; the clinical syndrome of culture-negative endocarditis remains on the differential diagnosis of patients with FUO, but is uncommon; proportion of undiagnosed patients has increased over time; diagnostic evaluation may fail to identify an etiology in 30-50% of patients; in many studies, patients have a good prognosis; approach to these patients includes a thorough history, physical exam, and a thorough travel history; infections to consider on the differential for patients with FUO include occult abscesses, atypical presentations of vertebral osteomyelitis, and tuberculosis; always have a high index of suspicion to diagnose tuberculosis, especially in those with extrapulmonary disease or who are immunocompromised and may present atypically; non-infectious causes include occult malignancy, drug fever, many rheumatologic disorders, and hereditary periodic fever syndromes; consider these diagnoses when patients report recurrent fever with fever-free periods of at least 2 weeks

High-value care statement: "When a patient has been reasonably evaluated — laboratory studies, repeat blood cultures, imaging studies — for ongoing fever, a diagnosis of fever of unknown origin should be reached and the patient should be observed in case further interventions would be appropriate later"

Suggested Reading

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Lung Infections

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Pneumonia

Introduction: affects ~450 million persons/yr globally (~7% of population); ~4 million deaths/yr; mortality declined in past decades, largely because of effective antimicrobial therapies and vaccine programs in developing countries

Pneumonia: airways(bronchi) tubular structures that branch down to small alveolar sacs (gas-exchanging units of lung) within terminal bronchioles; in cross-section, alveolar sacs associated with blood vessels; during infection, mucus, red and white blood cells and inflammatory exudate fill alveolar sacs and replace air, impairing gas exchange, resulting in dense consolidation; increasingly fills with inflammatory exudates, resulting in airless lung; *lobar pneumonia* — most common form, affects focal area; 2 types of diffuse pneumonia; *bronchial pneumonia* — patchy bilateral infiltrate in lung, usually reflects more severe disease, associated with immunocompromised states; seen more often in patients with neurologic deficits or those prone to aspiration; *interstitial pneumonia* — reticular nodular pattern of infiltrate; typically seen in atypical pneumonias (*ie*, caused by *Mycoplasma* and *Chlamydia*)

Signs and symptoms: fever (usually), leukocytosis, dyspnea, infiltrate on imaging studies; in children and younger adults, respiratory symptoms include shortness of breath, productive cough (sometimes rusty sputum), pleuritic chest pain, fever, and chills; in elderly people, nonspecific symptoms (*eg*, confusion, fatigue, hypersomnolence)

Types: *community-acquired pneumonia (CAP)* — from not associated with hospitals or nursing homes; *hospital-acquired pneumonia (HAP) (nosocomial pneumonia)* — occurs >48 hrs after admission to hospital or within 7 to 10 days after discharge; *ventilator-associated pneumonia (VAP)* — type of HAP; typically occurs 48 to 72 hrs after endotracheal intubation; thought that endotracheal tube bypasses normal airway defense mechanisms against infection; secretions above cuff of endotracheal tube may be aspirated into lung, resulting in increased propensity for VAP; risk for VAP increases by 1% per ventilator day; *pneumonia in immunocompromised host* — patients with HIV/AIDS, low CD4 counts, or who have undergone solid or hematologic transplants; emergence of unusual and opportunistic pathogens (bacterial, viral, fungal); immunocompromised states associated with neutropenia or immune defects from chemotherapy

Epidemiology and risk factors: CAP one of most common infectious diseases worldwide, ~5 to 7 adult cases/1000 persons/yr in US; seasonal variation, most occurring in winter (in US); CAP incidence increases with age; higher incidence of CAP among men and blacks; host defenses, virulence of pathogen, and size of inoculum play role in whether or not pneumonia develops; *other risk factors* for recurrent pneumonias — preexisting chronic lung diseases (*eg*, chronic obstructive pulmonary disease [COPD], cystic fibrosis [CF]), bronchial obstruction secondary to primary bronchogenic carcinomas or metastatic disease; bronchiectasis, which may be associated with development of primary or recurrent pneumonias (many potential etiologies for bronchiectasis, including mucoid impaction, recurrent pneumonias, CF, foreign body aspiration, rheumatic diseases [*eg*, tracheobronchial amyloidosis or relapsing polychondritis]); congenital anatomic defects (*eg*, yellow nail syndrome, pulmonary intralobar sequestration, bronchomalacia); impaired mucociliary clearance associated with immotile cilia syndrome (primary ciliary dyskinesia), can occur with or without situs inversus (with situs inversus, Kartagener syndrome); Young syndrome; toxic fume inhalation; conditions that predispose patients to recurrent macro- or microaspiration (associated with use of sedating medications or anesthetics, dysphagia from esophageal lesions or esophageal dysmotility syndromes, alteration in level of consciousness from with primary central nervous system [CNS] disease [*eg*, strokes, seizures]; metabolic disorders (*eg*, malnutrition, uremia) associated with recurrent pneumonias; immunocompromising conditions associated with immunosuppressive medications, (*eg*, chemotherapy, chronic glucocorticoid use; immune compromise from solid organ transplants, hematologic stem cell transplants, HIV infections

CAPs: typical and atypical pneumonias; *typical:* usually occur with acute onset of symptoms; *atypical* — usually occur with more insidious symptoms ("walking pneumonia")

Causes of typical pneumonia: most common (30%-60%) organism of CAP *Streptococcus pneumoniae* — pathogens vary with geographic region; common etiology in postinfluenza and postviral pneumonia; severe infections in patients with functional or anatomic asplenia; vaccination reduces risk for and frequency of invasive pneumococcal disease; *Haemophilus influenzae* — at-risk patients include those with underlying chronic lung disease (*eg*, COPD, CF); *Staphylococcus aureus* — gram-positive organism causes 2% to 5% cases; associated with postviral and postinfluenza pneumonia; 2 major categories, *S aureus* pneumonia: community-acquired methicillin-resistant

S aureus (MRSA) and community-acquired methicillin-sensitive *S aureus* (MSSA); in US, community-acquired MRSA associated with severe necrotizing pneumonia, with mortality rate >60%; resistance thought to be mediated by Panton-Valentine leukocidin gene; *gram-negative bacilli* — uncommon cause of CAP, usually occurring in patients at risk for aspiration or with chronic underlying lung disease; patients typically present with severe pneumonias requiring intensive care unit (ICU), often have chronic underlying lung disease; these pathogens include *Klebsiella*, *Enterobacter* spp, *Escherichia coli*, *Pseudomonas*, *Serratia* spp, *Proteus* spp, and *Acinetobacter* spp; *Pseudomonas* pneumonia typical CAP caused by gram-negative rod, can become rapidly resistant to antibiotic monotherapy; other gram-negative organisms in typical CAP category *E coli*; *E coli* and *Proteus* are extended-spectrum beta-lactamase organisms, sensitive only to carbapenems; need to distinguish between typical and atypical pneumonias when considering antimicrobial therapies

Causes of atypical pneumonia: *Mycoplasma pneumoniae:* — usually young (in 20s-30s), healthy individuals; typically person-to-person spread via respiratory droplets; prodrome of upper respiratory tract infection followed by nonproductive cough and extrapulmonary symptoms (*eg*, low-grade fever, diarrhea, generalized malaise, myalgias, arthralgias, rash [typically maculopapular]); some severe cases may present with thrombocytopenia, myocarditis, hemolytic anemia (due to cold agglutinins), transaminitis, bullous myringitis; gram stains typically negative; diagnosis made by culture, PCR, or serology with IgM and IgG; chest x-ray usually shows unilateral segmental lobar infiltrates, but can have patchy and interstitial bilateral infiltrates; can cause interstitial pneumonia; *Legionella* spp: accounts for 1% to 10% of CAP cases, may occur as sporadic infection or as outbreaks; aerosol transmission; outbreaks associated with exposure to variety of aerosol-producing devices (*eg*, showers, grocery-store mist machines, air-conditioning cooling towers, whirlpool spas, fountains, water distribution systems); sporadic legionellosis constitutes majority of cases, source usually unknown; organism typically cannot be detected by gram stain; patients with *Legionella* pneumonia may present with high fever, rapid progression of clinical symptoms and radiographic findings; severe pneumonia associated with extrapulmonary manifestations of disease (*eg*, renal failure, gastrointestinal [GI] and neurologic abnormalities, transaminitis); may have electrolyte abnormalities, including hyponatremia; *Chlamydia pneumoniae* — now called *Chlamydophila pneumoniae*; milder form of pneumonia; slow onset, slow recovery, patients have cough, malaise for weeks to months; patients with COPD, asthma exacerbations at risk

Common associations (gleaned from history): in patient with history of alcoholism, pathogen probably *Streptococcus*, oral anaerobes, *Klebsiella*, *Acinetobacter* spp, or *Mycobacterium tuberculosis*; if history of COPD or cigarette smoking, probably *H influenzae*, *Pseudomonas aeruginosa*, *Legionella* spp, *Streptococcus*, *Moraxella catarrhalis*, or *Chlamydophila pneumoniae*; in bed-bound patients, *Klebsiella*; patients with history of aspiration, gram-negative enteric pathogens or oral anaerobes; patient with lung abscesses, community-acquired MRSA, oral anaerobes, endemic fungi, *M tuberculosis*, atypical mycobacteria; in patient with HIV infection, *Staphylococcus*, *H influenzae*, and *M tuberculosis* if early presentation; in patient with HIV infection and late presentation, *Pneumocystis jirovecii*, *Cryptococcus*, *Histoplasma*, *Aspergillus*, and atypical mycobacteria; if patient recently on cruise ship, *Legionella* spp; patient from southwestern US and nodular lesions on chest x-ray, *Coccidioides* spp, hantavirus; in patient with unrelenting cough for weeks, *Bordetella pertussis*; history of bat exposure or spelunking, histoplasmosis; history of exposure to goat, cattle, or sheep, Q fever caused by *Coxiella burnetii*; hunter, especially from Arkansas, tularemia; patient from Chicago, Mississippi Valley or Ohio Valley area, blastomycosis; if influenza active in community, influenza, *S pneumoniae*, *S aureus*, or *H influenzae*; history of structural lung disease (*eg*, bronchiectasis), *P aeruginosa*, *Burkholderia cepacia*, and *S aureus*; history of endobronchial obstruction, anaerobes, *S pneumoniae*, *H influenzae*, or *S aureus*; in context of bioterrorism, *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), or *Francisella tularensis* (tularemia)

Clinical presentation: age affects presentation; clinical symptoms usually systemic (fever, chills, rigor), respiratory symptoms; cough might be productive, with purulent or rusty sputum, especially if *S pneumoniae*; pleuritic chest pain (pleuritis), dyspnea; exam may reveal pyrexia, tachycardia (may be associated with paroxysms of atrial fibrillation), tachypnea, hypoxia (may have central cyanosis); lung exam might reveal focal rales, bronchial breath sounds, dullness to percussion, pleural rubs; chest x-ray may show small pleural effusions (parapneumonic effusions)

Differential diagnoses: in acute bronchitis, typically no evidence of consolidation on chest imaging; influenza, pulmonary embolism, pulmonary edema; primary bronchogenic carcinoma and metastatic lung disease symptoms similar to new-onset pneumonia (patients may have pneumonia as a superimposed disease process); acute respiratory distress syndrome (ARDS) may occur as consequence of pneumonia; drug toxicity may mimic clinical presentation and radiographic features of pneumonia; cryptogenic organizing pneumonia, pulmonary eosinophilia, acute bronchopulmonary aspergillosis, hypersensitivity pneumonitis, alveolar hemorrhage syndromes, and vasculitides can mimic signs and symptoms of pneumonia

Assessing severity of pneumonia: several scoring systems; most frequently used CURB-65 (**c**onfusion, **u**remia, **r**espiratory rate, **b**lood pressure); each entity gets 1 point for 6-point score (0-5); higher score means higher risk for death; patient with confusion: 1 point, urea >7 mmol: 1 point, respiratory rate >30/min: 1 point, blood pressure <60 diastolic: 1 point, age >65 yrs: 1 point; patient with score of 0 to 1: <3% mortality risk, can treated as outpatient; patient with score of 2: 13% mortality risk, moderate CAP, patient admitted; patient with score of 3: ~17% mortality risk, severe disease; patient with score ≥3: considered for ICU referral and management; other features with increased mortality risk -65include oxygen

saturation <92%, bilateral diffuse disease, septicemia, C-reactive protein >20%, severe comorbidities

Viral pneumonias: influenza pneumonia and respiratory syncytial viral (RSV) pneumonia most common; can be difficult to differentiate from bacterial pneumonias; can occur concomitantly with bacterial pneumonias; parainfluenza, adenovirus, and RSV can cause severe, sometimes fatal pneumonia in immunocompromised patients; coronavirus; hantavirus can cause severe respiratory disease, typically in patients who traveled to southwestern US; varicella pneumonia, most frequent complication of varicella infection in healthy adults (10%-30% fatality rate)

Key facts: some organisms (*eg*, *Legionella*, *M tuberculosis*, *Chlamydia*, *Histoplasma*) considered true pathogens when isolated; other organisms (*eg*, *Candida*, *S aureus*, enterococci, and *H parainfluenzae*), when isolated, considered colonizers, but can become true pathogens during immunocompromised states or with large inoculum; *pneumonia diagnosis* — generally requires compatible symptoms with infiltrate on chest radiographs

Staphylococcus: MRSA — incidence has increased since 1960s, when first described; now MRSA attributed to >60% *S aureus* isolated from ICU patients; MRSA accounts for ~90,000 infections/yr; resistance factor for MRSA related to penicillin-binding proteinase (PBP2A) encoded by mecA gene, which inactivates methicillin; MRSA can be hospital- or community-acquired form; community-acquired form very virulent; can cause skin and soft tissue infections, recalcitrant pneumonias; skin and soft tissue infections usually occur after exposure to contaminated gym equipment, where MRSA might exist as colonizer; outbreak of community-acquired MRSA in drug users in 1980s; virulence thought to be from Panton-Valentine factor, which produces leukocidin toxins; increased incidence of difficult-to-treat, severe necrotizing pneumonia; treatment may require surgical resection of portion of lung; risk factors include higher antibiotic exposure (especially cephalosporins, fluoroquinolones); increased incidence of community-acquired MRSA in HIV+ patients, patients with dialysis catheters, patients in long-term acute care facilities (colonization and poor hand washing); *treatment* — vancomycin, linezolid

Diagnostic workup for CAP: recommendations controversial; diagnostic investigations warranted when isolation of pathogen expected to significantly alter standard empiric management decisions; need for diagnostic testing gleaned from clinical and epidemiologic clues during initial evaluation; because low yield of cultures and results do not change management of CAP in outpatients, routine testing optional; Infectious Disease Society of America (IDSA) guidelines list indications/circumstances in which more extensive diagnostic testing may be indicated (*eg*, patients in ICU or with failed outpatient antimicrobial therapy, cavitary infiltrates, leukopenia, alcohol abuse, chronic severe liver disease, functional or anatomic asplenia, or when urine tests pneumococcus or *Legionella* antigen-positive; additional testing may be gram stain and sputum culture, bronchoscopically obtained bronchoalveolar lavage (BAL) fluid, tissue sampling of lungs with transbronchial biopsies

Laboratory tests: typically leukocytosis with left shift; white blood cell count may be depressed (especially in patients with severe shock or elderly); leukopenia portends poor prognosis; sputum cultures optional for outpatients with CAP (patients usually do well with empiric treatment); IDSA and American Thoracic Society 2007 guidelines state investigation for specific pathogens should be performed when pathogens suspected based on clinical and epidemiologic clues and when results will change management; *eg*, appropriate to test patients in ICU for *Legionella* and pneumococcal urinary antigens; blood and sputum cultures, as well as urinary antigen and/or other testing may be required in certain cases, *eg:* failure to respond to outpatient antimicrobial therapy; cavitary infiltrates; leukopenia at diagnosis and presentation; active heavy alcohol use; chronic severe liver disease; recent travel (within past 2 wks; should have tests appropriate for region of travel); severe obstructive or structural lung disease; anatomic or functional asplenia; pleural effusions (should also have thoracentesis with analysis of pleural fluid); if positive for pneumococcal urinary antigen, should have blood and sputum cultures; *serologic testing* — routine testing for *Legionella*, *S pneumoniae*, and *Chlamydia* not recommended but should be pursued in patients with specific indications; *bronchoscopy with BAL, brushings, washings, protective specimen brushings* — usually not done unless pneumonia severe or refractory to antimicrobial therapy; immunocompromised patients at presentation should have bronchoscopy with BAL; *procalcitonin* — reasonable adjunct to clinical judgment; procalcitonin (precursor of calcitonin) may be elevated during bacterial infection but decreased during viral infection; <0.1 mg considered low, favor decision to avoid or stop antimicrobial therapy

Vaccines: 2 major pneumococcal vaccines FDA approved in US; *PPSV23 (polyvalent 23 vaccine)* — capsular polysaccharide vaccine from 23 serotypes of pneumococcus responsible for 90% of invasive pneumococcal infections; shown to prevent invasive pneumococcal disease; IDSA recommends vaccinations with this vaccine for all immunocompetent patients aged >65 yrs and patients <65 yrs with diabetes, congestive heart failure, alcoholism, COPD, cirrhosis, asplenia, cerebral spinal fluid leaks, or who live in long-term care facilities; PPSV23 uses polysaccharide, so no protein (proteins needed for memory cells, so no memory developed with this vaccine); efficacy unknown in immunosuppressed patients but still recommended for patients with HIV, leukemia, lymphoma, or multiple myeloma as well as those who have had organ transplants or have had chronic steroid therapy; can be given simultaneously with other vaccines but at separate sites; revaccination recommended for patients >65 yrs who received initial vaccine >5 yrs prior; *PCV13 (Prevnar 13)* — pneumococcal protein-conjugate polysaccharide vaccine; can develop immunologic memory; stimulates good antibody response, mucosal immunity; herd protection and immunologic memory in adults and children; vaccination shown to decrease invasive disease in children and adults; not yet

recommended for healthy persons, especially adults, lack of proven efficacy in this group; some data suggest efficacy in immunocompromised patients; *those approved to receive sequential vaccination with both PCV13 and PPSV23* — patients with congenital or acquired immunodeficiency, HIV, chronic renal failure, hematologic malignancies (*eg*, leukemias, lymphomas, and multiple myeloma), nephrotic syndrome, and chronic renal failure, patients on immunosuppressive therapy, and solid organ transplant recipients; FDA approved PCV13 for all children aged <5 yrs and adults aged >65 yrs; children and adults aged 6 to 64 yrs of age with certain medical conditions recommended to have this vaccine; thought to decrease invasive pneumococcal infection; *influenza vaccine* — influenza infection can result in secondary bacterial pneumonia, commonly caused by *S pneumoniae*; people who should be vaccinated include all persons aged >6 mos; people in high-risk groups, including persons aged >65 yrs, residents of nursing homes and long-term care facilities, patients with chronic diseases (*eg*, diabetes, immunosuppression, hemoglobinopathies, chronic kidney disease), patients who can transmit influenza to other persons at high risk (*eg*, health care workers, household members of patients at high risk, employees of home health care, nursing home, and long-term care or assisted living facilities); vaccine recommended for persons aged 60 to 64 yrs

HAP (nosocomial pneumonia): organisms associated with HAP include common aerobic gram-negative bacilli, (*eg*, *Klebsiella*, *Enterobacter*, *Pseudomonas*, *Acinetobacter*) and gram-positive cocci such as *Staphylococcus* and *Streptococcus*; emergence of HAP and multidrug resistance; increased risk for multidrug-resistant organisms in patients who have received antibiotics in last 90 days, have been hospitalized for >5 days, from communities or hospital units with high frequency of antibiotic resistance, or immunosuppressed; *diagnosis* — similar to that for CAP, made on basis of new or progressive infiltrates on imaging, plus 2 of following: fever, purulent sputum, leukocytosis or leukopenia, increased oxygen requirements; *differential diagnosis* — similar to that of CAP; includes aspiration pneumonitis, pulmonary embolism with infarction, ARDS, pulmonary drug toxicity, cryptogenic organizing pneumonia, pulmonary hemorrhage syndromes, primary metastatic disease to lungs, radiation pneumonitis; blood cultures recommended for HAP; thoracentesis recommended for patients with large pleural effusions; lower respiratory tract samples obtained via bronchoscopic examination with BAL; quantitative cultures significant if >1 million colony-forming units (CFU)/mL for tracheobronchial aspiration and >10,000 CFU/mL for BAL specimens; for protected specimen brush samples, >1000 CFU/mL significant

Treatment: selected based on risk for suspected drug-resistant pathogens; regimen tailored when susceptibility data available; if *S aureus* or gram-negative bacilli (easily grown) not isolated from good-quality sputum specimens, discontinue coverage for them; coverage generally 7 days but ≤15 days if *Pseudomonas* cultured and ≤21 days if MRSA cultured; antimicrobial therapy duration extended based on clinical course, extent of infection, and response to treatment; if no multidrug-resistance risk factors, ceftriaxone, ampicillin, sulbactam, levofloxacin, moxifloxacin, ertapenem; if concern for resistant gram-negative bacteria, piperacillin with tazobactam or cefepime, or carbapenem (antipseudomonal drug) as monotherapy; if known multidrug-resistant risk factors, initiate cefepime, ceftazidime, imipenem, meropenem, doripenem, or piperacillin with tazobactam and antipseudomonal fluoroquinolone, aminoglycoside, or colistin; if MRSA suspected, add vancomycin or linezolid to regimen; treatments for those with CAP, third-generation cephalosporin plus macrolide, or fluoroquinolone (typically levofloxacin) as monotherapy; keep in mind side effects; fluoroquinolones and macrolides, prolongation of QT interval, may predispose patients to arrhythmias; fluoroquinolones associated with tendinitis and tendon rupture, particularly in elderly and those on chronic steroid therapy

Mycobacterial infections

M tuberculosis and atypical mycobacterial infections; lungs major site of *M tuberculosis* primary infection and disease; cause of CAP in developing countries and some regions of US; clinical manifestations of tuberculosis (TB) include primary, reactivation, laryngeal, and endobronchial TB; TB associated with lower-lung field infection and tuberculomas; pulmonary complications include hemoptysis, pneumothorax, extensive pulmonary destruction, bronchiectasis, malignancy, and chronic pulmonary aspergillosis within TB cavity

Primary TB: new TB infection or active disease in previously naive host; *symptoms* — fever most common (~70%), gradual onset, low-grade, can be 39ºC/102.2ºF, lasts 14 to 21 days; by 10 wks, fever usually resolves; ~50% patients have pleuritic chest pain, evidence of pleural effusion, (typically small on initial presentation); radiographic findings include hilar adenopathy, pleural effusions, pulmonary infiltrates; perihilar infiltrates may be seen; lower- and upper-lobe infiltrates typical, occurring in ~33% patients; in some patients, chest radiograph normal; natural history after primary infection in patients with intact immunity includes control of initial infection, entering into latent phase; ~10% patients have progressive primary pulmonary disease with TB pneumonia and expansion of infiltrates at site of initial seeding or near hilum; may also have hilar lymphadenopathy or disease at more distant sites (cervical lymphadenopathy, pericarditis, meningitis, miliary dissemination); disease progression after primary infection typically occurs in patients with poor immune response (*eg*, HIV patients, patients with chronic kidney failure, diabetes, or are on chronic immunosuppressive therapies, including glucocorticoids)

Reactivation TB: multiple names, including postprimary disease, recrudescent TB, endogenous reinfection, adult-type progressive TB; occurs in 90% adult cases; in HIV-uninfected individuals, results from reactivation of previous focus of mycobacterial containment seeded at time of primary infection; apical posterior segments of right upper lobes or superior segment of lower lobe of lung frequently involved, for unknown reason, but may be from relatively poor lymphatic flow in apices of lung; *M tuberculosis* may prefer higher oxygen tensions in apical areas of lungs; original site of

infection may have been visible as small scar (Simon focus); reactivation TB may remain undiagnosed and potentially infectious for ≥2 yrs, with development of symptoms only late in disease course; *symptoms of reactivation TB* — typically begin insidiously, present for wks or mos before diagnosis; most (~50%-67%) patients develop cough with weight loss and fatigue; cough may be absent or mild initially, nonproductive or productive of scant sputum; as disease progresses, cough becomes more continuous throughout day and productive of yellow, yellow-green, or blood-streaked sputum, may be foul smelling; symptomatic patients typically have smear-positive sputum; frank hemoptysis due to caseous sloughing or endobronchial erosion occurs later in disease, rarely massive; dyspnea common, correlates with extent of parenchymal involvement, size and appearance of pleural effusions, and/or development of pneumothorax; pleuritic chest pain not common but, when present, signifies inflammation abutting or invading pleura with or without pleural effusion; rarely progresses to frank empyema; ~50% patients have night sweats with fever (usually low grade at onset, may become higher as disease progresses); fever classically diurnal with afebrile period early in morning and gradually rising temperature throughout day, reaching peak in late afternoon or evening; fever usually subsides with sleep, but night sweats may occur and wake patient up; anorexia, malaise, and consumption (wasting) common features, especially in advanced stages; ~33% patients report chest pain and dyspnea, ~25% report hemoptysis; without treatment, patients may develop painful ulcers of mouth, tongue, larynx, and GI tract due to chronic expectoration, swallowing of infectious secretions (rare in setting of anti-TB therapy); *conditions affecting presentation* — comorbidities (*eg*, diabetes), administration of tumor necrosis factor alpha inhibitors, advanced HIV infection; those patients have more symptoms, higher proportion have smear positivity, cavitation, treatment failure, and non-TB deaths; *physical findings of pulmonary TB* — not specific, usually absent in mild and moderate disease; patients may have dullness to percussion on physical examination and decreased vocal fremitus on lung exam (typically indicates pleural thickening or effusion); crackles can be heard throughout inspiration when large areas of lungs involved; may be signs of consolidation with open bronchi, *eg*, whispered pectoriloquy, tubular breath sounds; hollow breath sounds heard over cavities (aphoric); extrapulmonary signs include clubbing, findings localized to other sites of involvement; *diagnostic testing* — routine hematology and biochemistry laboratory studies often normal in pulmonary TB; CRP elevated in ≤85% patients; hematologic changes can be seen late in disease, may include normocytic anemia, leukocytosis, monocytosis (rare); hyponatremia, usually associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH), rarely associated with adrenal insufficiency; hypoalbuminemia and hypergammaglobulinemia late findings; imaging of reactivation TB, apical posterior segments of upper lobe shows scarring or consolidation; consolidation may also be seen in superior segment of lower lobes and (rarely) in anterior segments of upper lobes; in ~20% of cases cavities seen with visible air fluid; some patients have hilar lymphadenopathy, infiltrates or cavities in middle or lower lung, pleural effusions, solitary nodules; these atypical in reactivation TB, more common in primary TB; fibrocalcific changes in upper lobes in ~5% of patients, indicative of healed primary TB; CT scan more sensitive than plain film in evaluation of TB

Endobronchial TB: involves tracheobronchial tree; may occur via direct extension to bronchi from adjacent parenchymal focus or via spread of organisms to bronchi via infected sputum; lesions more likely observed in main and upper bronchi; lower trachea involved in ~5% patients; endobronchial disease more common in patients with extensive pulmonary TB with cavitary lesions; before anti-TB therapy, endobronchial TB common in both primary and reactivation TB; *complications* — endobronchial TB may lead to bronchial stenosis; early diagnosis and treatment before fibrosis occurs reduces likelihood; bronchial obstruction, atelectasis with or without secondary infection, bronchiectasis, tracheal stenosis, and impingement of enlarged lymph nodes on bronchi; *presentation* — productive cough, chest pain, hemoptysis, lethargy, fever, dyspnea; may be acute in onset, may be confused with bacterial pneumonia; can be subacute or chronic, resembling bronchogenic carcinoma; may have barking cough (distinctive, occurs in ~67%), bronchorrhea (rare), wheezing, hemoptysis; lymph node rupture may result in associated chest pain; *diagnosis* — endobronchial lesions can exist without extensive parenchymal abnormalities; normal chest radiograph in ≤20% of patients; CT scan may show endobronchial lesions or stenosis, rarely fistulas; bronchoscopic exam usual modality for diagnosis; findings include edematous, hyperemic lesions with or without ulceration or fibrosis within bronchus; tuberculomas, rounded mass-like lesions that develop during primary infection or when focus of reactivation TB becomes encapsulated; cavitation rare; differential diagnosis of pulmonary coin lesions extensive; diagnosis of tuberculoma difficult, since airway cultures often negative

Suggested Reading

Cavallazzi R et al: Predicting *Mycobacterium tuberculosis* in patients with community-acquired pneumonia. *Eur Respir J*. 2014;43(1):178-84; **Grief SN, Loza JK:** Guidelines for the evaluation and treatment of pneumonia. *Prim Care*. 2018;45(3):485-503; **Ottosen J, Evans H:** Pneumonia: challenges in the definition, diagnosis, and management of disease. *Surg Clin North Am*. 2014;94(6):1305-17.

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Tuberculosis and Pneumonia

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Overview of treatment for pneumonia: guidelines exist regarding treatment decisions about antimicrobial treatment

- Previously healthy patient with community-acquired pneumonia (CAP), treated as outpatient: no prior risk factors for drug-resistant infection, so can be safely treated with empiric macrolide antibiotic (*eg*, azithromycin [AzaSite, Zithromax]) or respiratory fluoroquinolone (*eg*, ciprofloxacin [*eg*, Cetraxal, Cipro, Otiprio) as monotherapy
- Patient hospitalized but not requiring ICU: monotherapy with fluoroquinolone or combined therapy with beta-lactam and macrolide (*eg*, azithromycin)
- Hospitalized patient with CAP requiring ICU care: treat with dual antimicrobial therapy; can include third-generation cephalosporin plus macrolide, alone or in combination with fluoroquinolone
- Other treatment options: patients at risk for *Pseudomonas* should receive antipseudomonal antimicrobial therapy plus aminoglycoside with macrolide or fluoroquinolone; when MRSA suspected, guidelines suggest adding vancomycin (Vancocin), linezolid (Zyvox), or ceftolozane plus tazobactam (Zosyn]) to antimicrobial regimen; for CAPs caused by atypical pathogens (*eg*, *Mycoplasma pneumoniae*), macrolide or tetracycline preferred, fluoroquinolones can be used as alternative; preferred treatment for *Legionella* species fluoroquinolone or azithromycin, with doxycycline (*eg*, Doryx, Monodox, Vibramycin) as alternative; preferred treatment for *Chlamydia psittaci* tetracycline (*eg,* Achromycin V, Panmycin, Sumycin), with macrolide as alternative

Fungal Pneumonias and Related Mycoses

Overview: major categories include pneumonias caused by endemic pathogens and those caused by opportunistic mycotic pathogens

Endemic mycoses

Coccidioidomycosis: typically occurs in patients who have spent time in southwestern United States, including southern California and parts of Arizona; major species *Coccidioides immitis* (causes valley fever); human and soil forms; human form noninfectious, soil form infectious; infections associated with soil form occur when soil disturbed; construction, agricultural, and field workers at risk, as well as residents of or visitors to southwestern US

- Symptoms: typically occur 1 wk to 4 wks after exposure; presents with lobar pneumonia that can spontaneously remit; occasionally rupture into pleural space if subpleural infection, causing empyema; diffuse pneumonia can occur, typically from large inoculum
- Chronic fibrocavitary disease: form of pulmonary disease that can occur with coccidioidomycosis; formation of pulmonary cavities, can be quite large; patients may also have interstitial fibrotic changes; *risk factors* — immunocompromised patients (including those with HIV) may develop disseminated disease); also patients with diabetes and preexisting lung disease
- Diagnosis: *x-rays* — may show diffuse reticular nodular infiltrates or miliary pattern of infiltrates on CT scans; may spread to bones, central nervous system (CNS), joints, and skin; *laboratory tests* — serologic testing required; positive ~90% of time; correlates well with disease activity; *Coccidioides* complement-fixation testing, tube precipitin testing; cultures from skin and bone helpful; histologically, organism appears as giant spherules with many tiny endospores
- Treatment: mandatory if immunocompromised; if intact immune system and only evidence of stable cavity, no specific indication to treat unless cavity starts to enlarge or symptoms such as hemoptysis develop; fluconazole (Diflucan) or itraconazole (Onmel, Sporanox) for limited disease; amphotericin B (Amphocin, Fungizone) preferred for diffuse pulmonary disease or disseminated disease; patients with meningitis also should be treated with amphotericin B (intrathecal for initial therapy) followed by lifelong azole therapy with fluconazole

Histoplasmosis: *Histoplasma* dimorphic fungus (mold in soil, yeast in human host); intracellular organism; major species for lung problems *Histoplasma capsulatum*; endemic in Midwest and south-central US, Ohio and Mississippi River valleys

- At-risk groups: spelunkers (those who visit caves with bats, exposed to bat guano); persons who handle chickens and chicken coops; found in and around decaying trees
- Transmission: through inhalation of airborne droplets; droplets get into respiratory system and travel to hilar and mediastinal lymph nodes
- Symptoms: immunocompromised patients have increased risk of severe disease; otherwise, relatively asymptomatic
- Diagnosis: based on sputum; *laboratory tests* — bronchoalveolar lavage (BAL) cultures (tends to grow well); tissue biopsies helpful for confirmation; not colonizer, so if isolated, pathogen; urinary and

serum *Histoplasma* antigen >90% sensitive for acute disease, so helpful in diagnosis; complement-fixation testing helpful (test remains positive for years after acute infection); increased titers correlate with disease severity; *imaging studies* — may show diffuse multinodular infiltrates, which may be confused with miliary pattern associated with tuberculosis (TB), but nodules tend to be somewhat bigger and better defined; mediastinal lymphadenopathy; lymph nodes can sometimes calcify (calcified granulomas can be seen on biopsies)

- Forms of disease: acute, subacute, and chronic forms; in acute forms, symptoms typically <1 mo; in subacute forms, symptoms typically >1 mo; fever, chills, malaise, cough, and pruritus
- Complications: may include pericarditis and effusions; can develop unique skin lesions, erythema nodosum; polyarthritis another feature; disease may progress to acute respiratory distress (ARDS) in patients with disseminated and severe disease; other complications include mediastinal granulomas and fibrosing mediastinitis; *fibrosing mediastinitis* — not caused by proliferation of organism itself but by release of histoantigen; associated with pulmonary hypertension and many signs and symptoms, including superior vena cava syndrome; liver and spleen calcifications helpful in diagnosis (if cultures negative but liver and spleen calcifications, can help with diagnosis)
- Treatment: itraconazole for mild to moderate disease; amphotericin for more severe disease addition of methylprednisolone (Medrol) may be helpful)
- Chronic cavitary histoplasmosis: typically, uniformly positive cultures; treated with itraconazole for protracted period (≥12 months)
- Progressive disseminated histoplasmosis: fairly rare; seen in patients with impaired T-cell function; patients should be hospitalized and treated with liposomal amphotericin B for 1 wk to 2 wks, then lifetime itraconazole; use and utility of steroids in patients with progressive disseminated histoplasmosis controversial but has been recommended in severe cases

Blastomycosis: similar geographic distribution to histomycosis; endemic in Mississippi and Ohio Valley areas; less common than histoplasmosis; one of least common forms of endemic mycoses; soil contaminant; pathogen *Blastomyces dermatitidis*

- Symptoms: typically mild, mimicking acute bacterial pneumonia; fever, cough, and shortness of breath; typically no weight loss or night sweats; disseminated disease may occur in immunocompromised patients; can travel to brain, skin, bone, and genitourinary (GU) tract; in skin, characteristic pustules, and papules, and subcutaneous nodules; disseminated form may progress to ARDS
- Diagnosis: urinary antigen and serum antigens helpful, positive in 90% of cases of disseminated disease; cultures definitive, but organism hard to grow and poorly sensitive; histologically, broad-based, budding yeast on wet preparation under microscope
- Treatment: surveillance in relatively asymptomatic patients; in those with symptomatic pulmonary disease and/or disseminated disease, itraconazole or amphotericin for severe disease (preferred for severe disease)

Sporothrix schenckii: soil contaminant, typically found in decaying soil; typically causes disease through cutaneous inoculation; typical scenario, woman gardening in rose garden, pricks finger with rose thorn and develops lymphocutaneous erythematous lesion that marches up arm; pulmonary disease rare; when pulmonary disease occurs, usually from inhalation of spores; can lead to chronic fibrocavitary disease; increased risk in individuals with history of significant COPD, alcoholism

- Diagnosis: cultures of skin lesions or sputum typically positive; histopathologically, mixed granulomatous and pyogenic organisms causing significant inflammation
- Treatment: itraconazole for 12 mos; amphotericin if severe

Opportunistic mycoses:

Aspergillus: ubiquitous dimorphic organism, causes aspergillosis; responsible for >50% of human opportunistic fungal infections; *A fumigatus* most common; others include *A niger*, *A terreus*, and *A flavus*

- Disease: can cause wide spectrum of lung diseases, which appears in correlation with immune status; in healthy patient with intact immune system; *allergic bronchopulmonary aspergillosis (ABPA)* — finger-glove distribution of upper-lobe infiltrates; typically caused by reaction to *Aspergillus*; treated with steroids; *aspergillomas* — seen as immune system becomes compromised; can cause chronic cavitary disease; *semi-invasive aspergillosis (chronic necrotizing aspergillosis)* — associated with further immune-system decline; *invasive pulmonary aspergillosis and tracheobronchial aspergillosis* — seen in severely immunocompromised patients
- Evaluation: *x-rays* — may show nodules that may cavitate; nodules may be associated with halo sign and/or air crescent sign; *laboratory tests* — nodules appear histologically as septate hyphae that branch at 45° angle; galactomannan enzyme immunoassay (EIA) detects components of fungal cell wall; sensitivity varies from 40% to 90%, depending on immune status, prior antifungal therapy, and infection severity
- Treatment: voriconazole (Vfend), amphotericin B, or posaconazole (Noxafil, Posanol); *A terreus* not sensitive to amphotericin

Cryptococcus: *C neoformans* major pathogenic organism; budding encapsulated yeast; most commonly presents with meningoencephalitis; may cause pulmonary nodules **(**typically asymptomatic**)**

- Diagnosis: based on India ink stains, especially on cerebrospinal fluid, looking for cryptococcal antigen; India ink stain helpful in diagnosing disease in patients with disseminated cryptococcal disease, but limited in those with focal pulmonary disease only; halo appearance seen on BAL fluid characteristic
- Treatment: fluconazole, typically 6 mos to 12 mos; for severe disease, amphotericin for 2 wks to 4 wks, then fluconazole for 8 wks, followed by fluconazole maintenance therapy for up to 1 yr; all immunocompromised patients with pulmonary cryptococcal infection require CNS disease workup with lumbar puncture

Mucormycosis: *Rhizopus mucor* and *Rhizomucor* comprise 70% of mucormycoses (collectively called zygomycetes); ubiquitous in soil; transmission through inhalation of conidial spores; can cause extensive

angioinvasive disease leading to vessel thrombosis and tissue necrosis that crosses tissue planes; second leading cause (after *Aspergillus*) of fungal pneumonias in immunocompromised patients

Symptoms: cough, high fevers, dyspnea, hemoptysis; similar clinical presentation to aspergillosis; more often have sinopulmonary infections with necrotic lesions within nasopharynx and endocranial soft tissues

Risk factors: iron overload states, immunocompromised states, poorly controlled diabetes, recent antifungal therapy for Aspergillus

Complications: formation of mycotic aneurysms and pseudoaneurysms; bronchial obstructions, particularly in patients with diabetes

Diagnosis: imaging typically shows multiple pulmonary nodules; some may cavitate; air crescent and halo signs can be seen, but less frequently than with *Aspergillus*

Bacterial Infections

Actinomyces: gram-positive anaerobe; forms sulfur granules (unique); part of normal oral flora, so isolation does not necessarily connote pathology; cause mass lesions with associated lymphadenopathy, sometimes bronchiectasis; tend to be pleural based, can cause pleural thickening; lesions can rupture into pleural space, causing empyema formation; *clue (along with formation of sulfur granules)* — chest-wall lesions that can invade or erode through chest wall; may be associated with facial osteomyelitis, particularly in alcoholics and those with poor dental hygiene or who have had recent dental procedures

Diagnosis: based on finding sulfur granules on BAL fluid or on tissue biopsies, including transbronchial biopsies or open lung biopsies

Treatment: penicillin drug of choice; also doxycycline, macrolides, clindamycin (Cleocin), and imipenem (Primaxin); occurs in immunocompetent patients, as opposed to Nocardia (typically occurs in more immunocompromised patients)

Nocardia: weakly acid-fast, gram-positive rod; soil contaminant; forms nodules that may cavitate; can cause bilateral multifocal pneumonia; pleural effusions can be seen; may result in empyema; more often seen in immunocompromised patients than *Actinomycetes*; can spread to skin, bone, brain, and muscles hematogenously; slow-growing organisms

Treatment: sulfamethoxazole and trimethoprim (Bactrim, Septra, Sulfatrim) first-line; other antimicrobials include minocycline, (*eg*, Akamin, Arestin, Minocin) linezolid, and cephalosporins; treat for extended time, usually 6 mos to 12 mos; if isolated, pathogen

Mycobacterial Organisms

Overview: include organisms responsible for *Mycobacterium tuberculosis* and nontuberculous mycobacterial organisms

***Mycobacterium tuberculosis* (MTB):** resurgence in 1980s and 1990s; correlated with increased HIV epidemic; transmission through airborne droplet nuclei expelled by coughing or sneezing; increased transmission rates associated with increased concentration of acid-fast bacilli (AFB)-positive organisms in sputum, in patients with cavitary disease, who cough frequently, in persons who live in crowded environments, and who have intimate contact with infected persons; ultraviolet (UV) light removes from environment; progression relies on compromised cell-mediated immunity

Risk factors: most important risk factors for development of active TB following exposure include host's response to infection and size of inoculum; other risk factors include time since exposure, with highest rates of development within first yr after initial exposure; HIV-seropositive patients have impaired cellular immunity, thus increased susceptibility; increased rate and risk of TB development in those treated with tumor necrosis factor alpha (TNF-A) blockers, which interfere with cellular immunity; disease states such as silicosis increase susceptibility; also patients on hemodialysis and those with diabetes; occurs at age extremes; children and persons aged >65 yrs have marked increased risk

Symptoms: cough most common and most prominent symptom; tends to be dry initially; as disease progresses, associated tissue necrosis within lungs; productive cough, even productive of blood, may develop; systemic symptoms include fever, malaise, and weight loss; may present with hyponatremia that has been associated with development of syndrome of inappropriate antidiuretic hormone secretion (SIADH); leukocytosis also common

Imaging: typical finding in primary tuberculosis, imaging studies show infiltrates that predominate in middle and lower lung zone with associated ipsilateral lymphadenopathy; in reactivation TB, upper lobe–predominant disease primary finding; may be associated with cavitation; calcified, fibrotic scars; may be associated with volume loss as lesion heals; erosion into lymph nodes or blood vessels may herald dissemination that may show on imaging as miliary pattern; significant hemoptysis can occur

Prevention: attempts to prevent TB by prescribing bacillus Calmette-Guerin (BCG) in developing and high-prevalence countries; efficacy of BCG in prevention not well documented; never give to immunocompromised persons, including HIV seropositive or pregnant

Tuberculin skin test: standard test; used for yrs in assessing whether significant exposure to TB; uses 0.1 cm^3 of 1/1000 mg of purified protein derivative injected under skin; reaction read within 48 hrs to 72 hrs; diameter of induration (not diameter of surrounding erythema) read; positive test suggests significant exposure to TB; cannot distinguish latent TB from active infection

Positive purified protein derivative (PPD) skin test: definition varies; in HIV-positive patients, those with other significant immune suppression, or with exposure to close contact with person with active TB, cutoff for positivity >5 mm induration; in recent immigrants, health care workers, persons who engage in intravenous drug use, and those with comorbid illnesses, cutoff for positivity 10 mm; >15 mm positive for others

Interferon-gamma release assay: more recent test for assessing significant exposure; cannot distinguish latent vs active disease; appears to be more specific than PPD skin test in those with prior BCG vaccinations; however, overlaps with some nontuberculous mycobacterial organisms and yields false positives in this setting; must be processed within 12 hrs of collection

Other diagnostic techniques: culturing organism on BAL fluid or on tissues definitive; positive polymerase

chain reaction (PCR) definitive; AFB stains suggestive of mycobacterial disease but not definitive for *M tuberculosis*

Treatment: *culture-positive patients not previously treated* — standard therapy includes RIPE 4-drug therapy (rifampin [Rifadin, Rimactane], isoniazid [INH], pyrazinamide, and ethambutol [Myambutol]) for 2 mos, followed by INH and rifapentine for additional 4 mos; check sputum cultures monthly until 2 consecutive cultures negative

Drug-resistant TB: typically occurs with medication noncompliance or failure to complete full therapy course; definition of drug-resistant *M tuberculosis*, resistance to 2 standard drugs (*ie*, INH and rifampin); patients showing resistance to other antituberculous combinations not considered drug resistant; another category of extensive mycobacterial drug resistance, in patients who show resistance to INH and rifampin as well as quinolones and ≥1 of 3 injectable second-line treatments (eg, amikacin [Amikin], kanamycin [Kantrex], capreomycin [Capastat]); extensive multidrug-resistant TB associated with increased mortality

Nontuberculosis mycobacteria: pulmonary disease caused by nontuberculous mycobacteria primarily from infection with *M avium* complex (MAC) and *M kansasii*

MAC: comprises 3 specific organisms, *M avium*, *M intracellulare*, and *M chimaera*; genetically similar; generally not differentiated in clinical microbiologic testing; most common cause of nontuberculous mycobacterial pulmonary disease

Signs and symptoms: variable and nonspecific; influenced by preexisting symptomatic lung disease (*eg*, cystic fibrosis, chronic obstructive pulmonary disease [COPD]); typically dry cough, malaise, generalized weakness, dyspnea on exertion, fatigue, occasionally bouts of hemoptysis; fever and weight loss less frequent than with typical TB; coexisting infections common; typically attributed to development of bronchiectasis; *major clinical presentations of MAC pulmonary disease* — 1. pulmonary disease associated with preexisting lung disease; primarily middle-aged white men with history of heavy alcoholism and/or tobacco use with associated COPD; typically resembles TB clinically and radiographically but symptoms less severe; relatively insidious onset and progression; 2. pulmonary disease that develops in nonsmoking women, typically aged >50 yrs; interstitial patterns on chest radiographs; Lady Windermere disease; typical presenting symptoms include cough, occasionally with purulent sputum; patients usually afebrile; weight loss not major feature; insidious symptom development; typically present 5 mos to 6 mos after onset of symptoms before diagnosis made; may have cavitation and adenopathy; associated with nodules and bronchiectasis, typically within right middle lobe and lingula

Diagnostic criteria: guidelines from American Thoracic Society (ATS) and Infectious Diseases Society of America (DSA); criteria for nontuberculous mycobacterial pulmonary infections include both imaging studies consistent with pulmonary disease and isolation of mycobacteria from sputum or from ≥1 bronchial wash in symptomatic patient; diagnosis of nontuberculous lung disease requires ≥2 positive cultures from sputum, 1 positive culture from bronchoscopic wash or lavage, or positive culture from transbronchial or other lung biopsy; compatible histopathologic features (*eg*, granulomatous inflammation or stainable AFB) and 1 positive sputum or bronchial wash culture for nontuberculous mycobacteria regardless of mycobacterial strain also helpful for diagnosis

Other forms of mycobacterial disease: "hot-tub lung," form of MAC-related lung disease felt to represent hypersensitivity pneumonitis; MAC may rarely present as disseminated disease, particularly in immunocompromised patients (those with HIV infection, immune suppressed following treatment for hematologic malignancies, and who have undergone immunosuppressive therapy including TNF-A inhibitors)

Treatment: limited data regarding optimal therapy, including duration; generally treated with macrolide plus ethambutol plus erythromycin for macrolide-susceptible disease; guidelines not well established (little data to support specific treatment algorithms); recommended that patients requiring therapy be treated by clinicians at centers equipped with reliable laboratory services for mycobacterial cultures and who have experience with management of these patients; treatment typically requires prolonged use of costly combinations of multiple drugs with significant potential for toxicity; macrolide-sensitive disease generally treated with multidrug regimen that includes macrolide plus ethambutol plus rifamycin; macrolide-resistant disease typically treated with ethambutol plus rifamycin plus parenteral aminoglycoside; linezolid or clofazimine may be added; diagnosis of MAC does not obligate therapy; make treatment decisions based on individual's potential risks and benefits and patient's clinical presentation; consider degree of symptoms and degree of compromise in lung function associated with organism; unlike pulmonary TB, surveillance may be reasonable, depending on individual patient

M kansasii: may be associated with significant lung disease; water contaminant; typically contaminates tap water in cities where endemic; may cause clinical symptoms and signs similar to TB; cavitation prominent feature; cavities tend to have thinner walls with less surrounding parenchymal infiltration than those associated with TB

Diagnosis: same criteria as for diagnosis of MAC-related lung disease

Treatment: typically requires multidrug regimen with rifampin, ethambutol, and INH or clarithromycin (Biaxin)

HIV-associated Pulmonary Diseases

Overview: correlates closely with degree of immune dysfunction; manifestations in setting of relatively normal immune function similar to general population; CD4 lymphocyte count accurately predicts risk of specific infections and neoplastic disorders in patients with HIV; *spectrum of pulmonary disease correlating with decline in immune function — Streptococcus pneumoniae*, significant cause of morbidity and mortality associated with bacterial pneumonias in HIV-positive patients regardless of antiretroviral

history; *Pseudomonas aeruginosa* and *Staphylococcus aureus* common causes of bacterial pneumonias in HIV population; treatment of *P aeruginosa* and *S aureus* as well as streptococcal pneumonia same as in non-HIV patients; persons with HIV should get vaccinated for streptococcal pneumonia

CD4 count and disease: as CD4 count declines, increased incidence of certain types of HIV-related diseases; with any CD4 count, association with bacterial pneumonias as well as non-Hodgkin lymphoma; with decline in CD4 count to <200 cells/mcL, increased frequency of bacterial pneumonias with associated bacteremia and disseminated TB, *Pneumocystis jiroveci* pneumonia, and cryptococcal pneumonias; with CD4 count <100 cells/mcL, emergence of bacterial pneumonias including *S aureus*, *Pseudomonas*, and neoplasms associated with Kaposi sarcoma and toxoplasmosis; at CD4 counts between 50 and 100, start to see increase in endemic fungi as well as cytomegalovirus (CMV) and *M avium cellulare*; both endemic and nonendemic fungi emerge

Mycobacterial disease and HIV: mycobacterial disease one of most common opportunistic infections; progression of latent to active TB in coinfected patients much higher than if HIV negative; HIV-infected patients should be tested for latent TB with tuberculin skin testing or interferon-gamma assays at time of HIV diagnosis and annually; patients coinfected with TB and HIV may develop immune reconstitution inflammatory syndrome (IRIS)

Drug reactions: occur with simultaneous TB and HIV treatment; include increased adverse reactions to protease inhibitors that may cause increase in disease relapse; thioacetazone (Neothetazone) may potentially cause fatal exfoliative dermatitis

Pneumocystis jiroveci pneumonia (PJP): one of most common AIDS-defining infections; common cause of AIDS-related pneumonia; treatment with sulfamethoxazole and trimethoprim for 21 days if mild to moderate infection; addition of steroids has some efficacy for severe disease, defined in this setting as Pa_{O2} <70 mm Hg or increased alveolar-arterial (A-a) gradient >35 mm Hg; patients with CD4 count <200 and oropharyngeal candidiasis should be treated with PJP prophylaxis 3 times/wk

Other fungi: other fungi and fungal diseases that may occur include *Cryptococcus*, coccidioidomycosis, *Histoplasma*, and invasive aspergillosis; any of these fungal pneumonias in setting of HIV may cause disseminated disease that can be life threatening

Viral pneumonias: common; CMV one of most common causes of viral pneumonias in HIV setting; typically causes problems with gastrointestinal (GI) tract and retina; may cause severe pneumonia, especially if CD4 count <50; isolation of CMV in BAL fluid not sufficient for diagnosis of CMV pneumonia (viral shedding from respiratory secretions common and may not indicate disease)

Parasitic infections: one of more common parasitic infections caused by Toxoplasma; typically leads to encephalitis; may have nonspecific pulmonary symptoms; patients who test negative should be instructed to avoid raw uncooked meats and to avoid cat feces

Recommendations

Treatment recommendations: IDSA and ATS have guidelines; recommend patients with CAP in good clinical standing, with good response to antimicrobial therapy, be treated for ≥5 days, up to 7 days; should be afebrile for 48 hrs to 72 hrs prior to discontinuation of antimicrobial drugs; should be breathing without use of supplemental O_2 unless patient required supplemental O_2 for preexisting lung disease prior to coming to hospital for treatment of CAP; should have no more than one instability factor defined as heart rate >100 beats/min, respiratory rate >24 breaths/min, and systolic blood pressure <90 mm Hg

Treatment extensions: treatment >7 days may be necessary in some patients; these include patients who do not meet requirements for discontinuation and patients in whom initial antimicrobial choices were not active against the subsequently identified pathogen; also may be needed in patients with extrapulmonary infection (*eg*, endocarditis, osteomyelitis, meningitis); patients with *P aeruginosa*, *S aureus*, *Legionella*, or other pneumonias caused by atypical or fungal pathogens may require longer duration

Testing recommendations: chest x-rays typically not recommended after completion of antimicrobial therapy in patients with uncomplicated pneumonia syndromes; some specialized cases, *eg*, patient aged 50 yrs with significant prior smoking history may require chest radiograph in 7 wks to 12 wks to confirm infiltrate going away and no concomitant problem (*eg*, lung or other cancer); for lingering infections, repeated chest radiographs at 7 wks to 12 wks following completion of antimicrobial therapy reasonable to rule out competing diagnosis (*eg*, organizing pneumonia) that may require additional therapies

General Points and Conclusions

Risk of pneumonia: increased with solid-organ or hematopoietic stem-cell transplantation; increased with lifestyle factors such as tobacco use, alcohol consumption, and toxic inhalations; homelessness and living in overcrowded conditions associated with outbreaks

Take-away points: 1. although many organisms may cause pneumonia, few associated with majority of cases; stratification into categories of CAP and hospital-acquired pneumonia (HAP) makes sense, informs clinicians of anticipated potentially causative organisms; knowledge of usual organisms associated with CAP and HAP key to management; 2. major effort to reduce pneumonia incidence=prevention; vaccines targeting influenza and pneumococcal disease mainstays, particularly for CAP; administer vaccines according to established guidelines

Suggested Reading

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HIV/AIDS Update

Roy Gulick, MD, *Professor of Medicine, Weill Cornell Medicine, New York, NY*

Epidemiology: first cases of acquired immunodeficiency syndrome (AIDS) described in 1981 in 5 homosexual men in Los Angeles area; reported in Centers for Disease Control and Prevention's (CDC) *Morbidity and Mortality Weekly Report* June 1981; as of 2019, >70 million people have been infected with human immunodeficiency virus (HIV) and more than half have died; ~37 million people living with HIV infection worldwide; Africa, particularly sub-Saharan Africa most affected, accounting for two-thirds of cases in world; however, HIV affects every country, true pandemic

North America: >1 million people living with HIV infection; recent trends in HIV favorable; people newly infected per yr peaked in 1995-1996 (>3 million people); today, just >1 million people per yr; number of HIV-related deaths rose every yr worldwide into mid-2000s, peaking at nearly 2 million deaths per yr; now <1 million per year; *United States (US)* — number of AIDS cases and AIDS-related deaths peaked in mid-1990s, then decreased by about two-thirds in 2 yrs, because of development of effective HIV therapy; AIDS rate and AIDS-related death rate since late 1990s continued to decline over time; number of people in US living with HIV highest ever (~1.1 million); newly diagnosed HIV cases in US per year once 40,000 to 50,000 cases but has declined in recent years; *eg*, from 2008 to 2015, number of new HIV cases declined by 15% (38,500 people); declines seen in several risk groups including heterosexuals and injection-drug users; cases of homosexual men have either plateaued or increased slightly

Breakdown of US newly diagnosed HIV cases: ~75% occur in men, ~25% in women; racial or ethnic groups most affected include African American and Hispanic or Latino populations; newly diagnosed HIV cases most affected proportionally young adults aged 25 to 44 yrs; adolescents and young adults aged 13 to 24 yrs also risk group for newly diagnosed HIV; homosexual men account for ~60% of newly diagnosed cases, heterosexual individuals ~25%, and injection-drug users now <10%; with US, areas highly affected include Northeast, far West, and increasingly South, including rural areas; HIV cases diagnosed in every state

Background: first isolated by 2 groups in 1983 and 1984; virus structure simple, with outer glycoprotein coat, inner protein coat that encases viral genetic material; RNA virus; reverse, or retrovirus; 2 types of HIV worldwide; most common, HIV-1; less common, HIV-2, confined to areas in western Africa or countries with traditional ties to western Africa, including Spain, Portugal, and several cities in India; subtypes or clades, go by letters of alphabet; clade B most common type seen in North America, Europe, and Australia; HIV infection zoonosis (*ie*, disease starts in animals and transmits to humans); in this case, likely monkey infection that crossed over to man in about 1900 AD; target cell for HIV is $CD4^+$ T lymphocyte, which plays central role in immune system by coordinating function of all other cells, leading to effective immune response; when number of T cells decreases over time from HIV infection, immune system becomes disorganized and suboptimal leading to profound immunosuppression

Diagnosis: previously tested for HIV antibody; this test developed in 1985, initially used to screen blood supply; today, use screening test, enzyme-linked immunosorbent assay (ELISA) test, tests for antibodies to HIV-1 and HIV-2; if ELISA repeatedly positive, perform confirmatory test; previously, confirmatory test Western blot, but expensive and complex

Newer tests: now use immunoblot test, which specifically tests for antibodies to HIV-1 or HIV-2; in resource-poor countries, may use rapid test as screening test, then second rapid test made by different manufacturer to confirm; testing can be done on either blood or oral secretions; 20-min tests readily available; 1-min blood test also available; can also test for presence of virus directly via viral protein, called p24 antigen; also, new combination screening test that screens for both antibodies to HIV and p24 antigen, allowing detection of virus earlier; another common way to test for viral presence, to detect and quantitate HIV RNA counts (viral load test); *window period* — length of time between exposure to virus and development of positive test; with older antibody tests, window period 3 mos; newer technologies provide shorter window period, particularly tests for HIV presence, ~2 wks

Current CDC recommendations for testing: routine, voluntary HIV screening for all persons aged 13 to 64 yrs in health care settings, not based on risk; for those with known risk factors, repeat HIV screening recommended at least annually; current screening recommended as "opt-out" in normal medical care (*ie*, opportunity for patient to ask questions and option to decline testing); specific consent for HIV testing no longer recommended or required

US Preventive Services Task Force (UPSTF) recommendations: screen adolescents and adults aged 15 to 65 yrs, screen all pregnant women, and screen younger adolescents or older adults if at increased risk for HIV infection; UPSTF grade A recommendation (*ie*, high certainty that net benefit substantial for screening for HIV infection); t private insurance and Medicare must offer these services without copay

Risks for HIV transmission: blood transfusion from HIV+ source to HIV– person, high risk of transmission, resulting in infection in ~9 of 10 exposures; needle sharing from injection-drug use from HIV+ source to HIV– person results in infection or seroconversion in ~1 in 167, or ~0.6% of exposures; percutaneous inadvertent needle stick in health care settings results in infection from HIV+ source in ~1 in 500 exposures; worldwide, sexual exposure most common way of transmission; among sexual practices, receptive anal sex most likely route of transmission; 1 in 70 exposures from HIV+ person will result in HIV transmission; insertive anal sex results in transmission 1 in 1000 times; receptive penile-vaginal sex, 1 in 1250 times; insertive penile-vaginal sex, 1 in 2500 times; oral sex thought to be low-risk exposure; transmission from infected mother to child occurs, in absence of therapy, in ~1 in 4 exposures

Workup for HIV: upon diagnosis, standard medical history and physical exam recommended; perform laboratory tests to stage patient; obtain complete blood count, chemistries including liver function tests and fasting lipid levels, and urinalysis; HIV-specific tests include confirming HIV serology results, performing CD4 cell counts, performing viral load or HIV RNA test, and performing genotypic resistance testing; in certain patients, could also order HLA-B*5701 genetic screening test (screens for genetic marker associated with hypersensitivity reaction to antiviral drug abacavir; if HLA-B*5701 negative, low risk of such reaction); another specialized test for use in specific cases, coreceptor tropism assay (patients infected with either R5-tropic virus, which binds to CCR5 receptor on CD4 cell, or with X4-tropic virus which binds to CXCR4 receptor; some patients can be infected with mixed population); certain class of agents, chemokine receptor inhibitors, can be screened for by tropism test, which diagnoses which type of virus patient has

Screening for coinfections: cytomegalovirus (CMV) antibody; sexually transmitted disease testing (chlamydia, gonorrhea, and serologic test for syphilis); toxoplasmosis antibody; screening test for tuberculosis (TB) infection (purified protein derivative [PPD] or interferon-gamma release assay [IGRA]) to assess for prior exposure to TB; viral hepatitis serologies for hepatitis A, B, and C; in select patients, consider sending serologies for varicella, measles, rubella, and mumps; cryptococcal antigen or acid-fast bacilli (AFB) blood culture not considered standard screening tests

Vaccinations: consider hepatitis A vaccine in patients with HIV who are homosexual men, use injection drugs, travel to areas endemic for hepatitis A, or have chronic liver disease from either hepatitis B or hepatitis C; hepatitis B vaccine should be offered based on results of serologies; human papillomavirus (HPV), new 9-valent vaccine, should be offered to both men and women with HIV infection aged ≤26 yrs; annual influenza vaccine should be offered; pneumococcal vaccine should also be offered, starting with protein conjugate vaccine with subsequent polysaccharide vaccine; routine tetanus-diphtheria-pertussis (Tdap) vaccine should be offered; primary varicella vaccine can be given if needed based on serology, if patient CD4 cell count >200 cells/μL; live virus herpes zoster vaccine can be offered if patient's CD4 cell count >200 cells/μL; no safety data for newer recombinant zoster vaccinations in HIV+ patients

HIV infection and AIDS: after infection, viremia (*ie*, number of viral particles in blood) reaches high levels within wks, potentially millions of copies of HIV RNA per mL of blood; level of virus in absence of therapy detected throughout course of HIV infection; target cell ($CD4^+$ T lymphocyte) count normally >400 cells/μL of blood; during acute infection, this cell count may decrease, then rebound; over course of infection, cell count declines; when decreases to 200 cells/μL, patient has profound immunosuppression, fulfilling current definition of AIDS; T-lymphocyte count can continue to decrease in absence of therapy, eventually to count of 0 cells/μL; mucosal T cells, associated with intestinal lymphoid tissue, decline by 80% within several wks of HIV infection, and in absence of therapy, do not rebound; HIV potent activator of immune responses; many of which dysregulated responses, which can lead to inflammation and ultimately end-organ damage, including diseases of heart, liver, kidney, nervous system, and non-AIDS cancers; average time from infection to progression to AIDS in US, without therapy, ~10 yrs; average time from diagnosis of AIDS (either CD4 count <200 cells/μL or occurrence of opportunistic infections) to death, ~1 to 2 yrs without HIV therapy

Opportunistic pathogens: complication of HIV; pathogens often nonpathogenic or of low pathogenicity and cause illness only in setting of profound immune suppression; can both treat for and provide prophylaxis for most

Pneumocystis carinii pneumonia (PCP): previously most common opportunistic infection associated with AIDS in US; also known as *Pneumocystis jiroveci* pneumonia; fungus; occurs with CD4 counts <200 (or, rarely, <300) cells/μL; presents as pneumonia, with shortness of breath and fever; thoracic radiograph typically features bilateral, patchy, interstitial infiltrates; hypoxia apparent; diagnosis by sputum or bronchoalveolar lavage (BAL) specimen using direct fluorescent antibody test to demonstrate organism; treatment of choice trimethoprim-sulfamethoxazole; alternative treatments pentamidine, primaquine, and clindamycin; prophylaxis effective and recommended if CD4 count <200 cells/μL, also with trimethoprim-sulfamethoxazole; alternative prophylaxis choices dapsone or atovaquone; can discontinue prophylaxis if CD4 count >200 cells/μL in patient on HIV antiretroviral therapy for at ≥3 mos, or if CD4 count >100 cells/μL after 3 to 6 mos of antiretroviral therapy with suppression

Toxoplasma gondii: parasite that can be reactivated in patients with profound immunodeficiency from HIV, CD4 count <100 cells/μL; typically causes focal neurologic lesions that may cause seizures or decreased mental status; diagnosis most often made clinically, plus *Toxoplasma* IgG titer (*ie*, antibody present in blood), and central nervous system (CNS) imaging study showing ring-enhancing mass lesions; magnetic resonance imaging (MRI) more sensitive than computed tomography (CT) scan for diagnosis; treatment often given empirically; treatment of choice pyrimethamine-sulfadiazine; alternative treatments pyrimethamine-clindamycin or trimethoprim-sulfamethoxazole; can be prevented; offer prophylaxis to patients who have CD4 count <less 100 cells/μL and positive *Toxoplasma* antibody titer; prophylaxis

of choice trimethoprim-sulfamethoxazole; alternatives either dapsone or atovaquone, combined with weekly pyrimethamine

Cryptococcus: fungus found commonly in environment; can cause meningitis in people with CD4 count <100 cells/μL; presents with common symptoms of meningitis (*ie*, fever, headache, neck stiffness); diagnosis made most frequently with organism visualization in cerebrospinal (CSF) fluid through lumbar puncture; blood cultures can also reveal presence of *Cryptococcus*; treatment of choice induction strategy with liposomal amphotericin B combined with flucytosine; alternative treatment fluconazole, with or without flucytosine; after several wks and clinical response, can change to maintenance therapy with oral fluconazole; if patient starts antiretroviral therapy, has virologic suppression, and reconstitutes CD4 count, can stop maintenance treatment

Mycobacterium avium complex (MAC): atypical *Mycobacteria* spp found commonly in environment; develop MAC disease if CD4 count <50 cells/μL; presents with fever, lymphadenopathy, hepatosplenomegaly, and weight loss; diagnosis made by sending AFB blood cultures, or occasionally by tissue biopsy with culture; treatment of choice macrolide antibiotic (*eg*, clarithromycin or azithromycin) together with second agent, ethambutol, and in many cases third agent, rifamycin (*ie*, rifampin or rifabutin); can provide prophylaxis for MAC infection; if CD4 count <50 cells/μL, can offer azithromycin or clarithromycin; more recent thinking, if patients start antiviral therapy, CD4 count will increase to >50, so prophylaxis may not be necessary

Mycobacterium tuberculosis: causes TB; most common opportunistic infection worldwide; can occur at any CD4 cell count; pulmonary TB generally most common presentation; with HIV infection, if CD4 count <200 cells/μL, extrapulmonary TB, essentially affecting any organ in body, can occur; treatment same as for patients without HIV infection; 4-drug therapy initially, with isoniazid, rifampin, pyrazinamide, and ethambutol, while awaiting drug susceptibility testing; with rifampin, drug-drug interactions with HIV medications can be complicated; no HIV protease inhibitors can be used with rifampin; dose adjustments for integrase inhibitors or potentially nonnucleoside reverse transcriptase inhibitors may also be necessary; can administer prophylaxis for TB; latent TB infections should be screened for with PPD or IGRA assays; once active TB ruled out, treat latent TB infection in HIV+ patients with isoniazid for 9 mos

Cytomegalovirus (CMV): viral illness seen in patients with CD4 count <50 cells/μL; most common presentation retinitis, with change in or loss of vision; can infect other organs, so can also present as colitis, hepatitis, or CNS disease; treatment of choice intravenous ganciclovir or oral valganciclovir; routine prophylaxis uncommon

Progressive multifocal leukoencephalopathy (PML): caused by JC virus; CD4 count <50 cells/μL; multitude of neurologic symptoms/signs; CNS scans reveal diffuse white-matter lesions; MRI more sensitive than CT; no effective therapy; antiretroviral therapy should be instituted because with immune reconstitution, PML can subside

Antiretroviral therapy: current guidelines recommend starting antiretroviral therapy when patient willing and has diagnosis of AIDS or symptomatic HIV disease, or when patient with HIV infection asymptomatic, with any CD4 count; now standard therapy for entire world; goal to suppress HIV RNA viral load level as low as possible, for as long as possible; thus can preserve or enhance immune function, typically assessed with CD4 count; patients can return to normal CD4 count levels; ultimate goal to delay clinical progression of HIV disease and prolong healthy survival; in 2019, 32 antiretroviral drugs available; most commonly use 3-drug regimens; antiretrovirals work by inhibiting points in HIV life cycle

HIV life cycle: when HIV first encounters CD4 cell, binds to $CD4^+$ receptor, then to second receptor called coreceptor (CCR5 or CXCR4); when these receptors encountered, virus membrane fuses with host-cell membrane, contents of viral particle enter cytoplasm; copies of viral RNA, along with viral-specific proteins (*eg*, HIV reverse transcriptase), transcribe viral RNA into viral DNA; 2 copies assemble to form complex, then with assistance from second viral specific enzyme, HIV integrase, viral DNA complex will enter cell and be inserted randomly into host-cell genome; HIV-infected host cell can live for 60 yrs (part of reason HIV difficult to cure); once viral genes integrated into host-cell genes, cells long lived, difficult to identify, and difficult to eliminate; cell can also be activated, genes transcribed into new copies of viral RNA, and also translated into viral proteins that assemble at cell surface and bud off into new viral particles; 1 infected cell can make hundreds to thousands of new copies of viral particles, or virions, many capable of starting this process in next host cell they encounter; post budding, third viral-specific enzyme, HIV protease, required for full maturation and infectiousness of viral particles; this enzyme cleaves viral polyproteins into required components; when enough viral particles have budded off host cell, integrity of cell membrane lost and cell dies; when enough T cells die, immune system becomes dysregulated and profoundly suppressed

Types of antiretrovirals: *reverse-transcriptase inhibitors* — oldest drugs; target virus early in life cycle; *nucleoside-analog reverse-transcriptase inhibitors* — look like 4 DNA bases; nonnucleoside reverse transcriptase inhibitors inhibit same enzyme (reverse transcriptase) but at distinct location from nucleosides; *HIV protease inhibitors* — third class, approved in 1990s; target enzyme (protease) late in life cycle; combinations of reverse transcriptase inhibitors and protease inhibitors used together, first effective treatments for HIV; *HIV fusion inhibitors* — target early step when viral particle fuses with host cell; but just 1 of 3 substeps of HIV entry; *candidate drugs for all 3 substeps* — chemokine receptor inhibitors and, more recently, post-CD4 attachment inhibitors; *HIV integrase inhibitors* — target middle step in life cycle, in which viral genes integrate randomly into host-cell genes; integrase inhibitors now optimal initial treatment for HIV because of their potency, convenience (given once daily), and relative lack of side effects or toxicities; today, 32 drugs in 5 different broad classes of drugs used to form treatment regimens; *triple-drug therapy* — most effective; in late 1980s, first antiviral agent approved (zidovudine [AZT]); use led to decreased HIV RNA levels, but then

levels rebounded, followed by AZT resistance; any positive effects short lived; mid-1990s, 2 nucleosides, used together, standard of care; decreased viral load level but again, rebound occurred within wks or mos, followed by resistance to both drugs; late 1990s, triple-drug therapy; decreased viral load level to below detectable levels, preventing emergence of drug-resistant virus; late 1990s, triple-drug combination therapies involved taking 20 pills divided every 8 hrs throughout day; complicated for patients; also associated with significant side effects; 2006, first single-pill, once-daily regimen for HIV with 2 nucleosides and 1 nonnucleoside (efavirenz); those types of regimens continued to be developed, and today >9 available, many in generic forms throughout world; either nonnucleoside based or more recently, integrase inhibitor based; first protease inhibitor–based, one pill, once daily approved in 2018

Guidelines: current US Department of Health and Human Services treatment guidelines suggests initial recommended regimen of choice for treatment of HIV infection, 2 nucleoside-analog reverse-transcriptase inhibitors, together with integrase inhibitor; can be coformulated into 1 or 2 pills; now considered standard of care for treatment of HIV infection

Monitoring: *CD4 count* — monitor CD4 count over time; obtain baseline assessment, then monitor every 3 to 6 mos at follow-up visits; after 2 yrs of antiviral therapy with virologic suppression, can decrease monitoring; if CD4 count has increased to 300 cells/μL to 500 cells/μL, can monitor count annually; if >500 cells/μL, optional, not necessary to continue to follow CD4 count as long as virologic suppression continues; *viral load* — assess viral load level at baseline, then at 2 to 8 wks after starting antiretroviral therapy to ensure patient's viral load reducing; once virologically suppressed, monitor viral load every 3 to 6 mos; after 2 yrs of suppression, monitor every 6 mos; *other monitoring* — perform drug-resistance testing (typically genotypic testing) at baseline to assess for evidence of transmission of resistant virus (occurs in ~17% of US patients); if positive, means patient acquired HIV virus with 1 or more drug mutations even though patient has never taken such drugs; also use genotyping to assess after virologic failure following either first or second antiretroviral regimen; virologic failure on third or later regimen becomes complicated; recommended to send both genotype and more expensive and complicated phenotype test; those drug-resistance results, together with antiviral history, used to try to develop next regimen

HIV patients today: population surveys show virologic suppression rates 80% or even higher; leading to immune reconstitution; ultimately, life expectancy of HIV+ patients appropriately treated now almost same as for general population; patients who started antiretroviral therapy with normal CD4 count, don't use injection drugs, and don't have viral hepatitis, life expectancy same as for general population; seen in developed countries, but also increasingly in developing countries; in 2018, >50% of 37 million people with HIV infection receiving antiretroviral therapy

90-90-90 goal: United Nations Programme on HIV/AIDS (UNAIDS); by 2020, goal to have 90% of all people living globally with HIV know their status, 90% of them to receive antiretroviral therapy, and 90% of them to have durable virologic suppression; many countries have achieved this goal so far

Prevention: *original approach* — "ABC" (abstain from sex, be faithful to your HIV+ partner, or use condoms and get counseled and tested); ABC approach worked for many people; today, bigger alphabet of additional strategies that have been proven; *male circumcision* — removing foreskin of penis (full of $CD4^+$ T lymphocytes), effective way of reducing risk of HIV infection by ~60% (shown in 3 different studies done in 3 different African countries); one of most effective ways to prevent HIV, use of antiretrovirals; *HIV+ pregnant women* — giving just single antiretroviral drug effectively reduced rate of transmission from 25% to 8%; triple-drug therapy has reduce risk to ≤0.5%; *other settings* — taking antiretrovirals to diminish viral load below detectable level reduces risk of transmission to others by >93%

Pre-exposure prophylaxis (PrEP): newer strategy to offer antiretroviral drugs to HIV–people but at risk of acquiring infection; 2 nucleoside analogs (tenofovir disoproxil fumarate and emtricitabine) coformulated in single pill; US Food and Drug Administration (FDA) approved this drug for PrEP in 2012; recent studies of PrEP, 1 in United Kingdom and 1 in France and Canada, showed PrEP led to >85% reduction in HIV infection

Cure: only 1 patient cured thus far; unusual case of male patient with well-controlled HIV infection, who then developed leukemia requiring bone marrow transplant; underwent total body irradiation and cytotoxic chemotherapy, had to stop antiretroviral drugs because of toxicity; underwent stem cell transplant, bone marrow transplant, rejected transplant, underwent antirejection medications, and received second stem cell transplant; after completing treatments, could no longer detect presence of HIV; CD4 count rebounded to normal levels; 9 yrs later, remains free of HIV infection

HIV vaccines: HIV vaccine challenging because effective immune response to HIV poorly understood; no natural example exists; 4 large vaccine studies performed, based either on eliciting antibody responses or cytotoxic T-lymphocyte responses, or both; 3 of those studies completely negative, showed no benefit; 1 study in Thailand showed ~30% reduction in risk of HIV infection, but further studies needed

Suggested Reading

Grande F et al: CCR5/CXCR4 dual antagonism for the improvement of HIV infection therapy. *Molecules*. 2019;24(3); **Waymack JR, Sundareshan V:** Acquired immune deficiency syndrome (AIDS). StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; Updated January 2019. Available from www.ncbi.nlm.nih.gov/books/NBK537293/; **Zicari S et al:** Immune activation, inflammation, and non-AIDS comorbidities in HIV-infected patients under long-term ART. *Viruses*. 2019;11(3).

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Health Advice for Travelers; Ticks and Tick-borne Infections

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Travel background: everybody travels; millions of Americans travel across borders, visit underdeveloped areas, and many will visit malarious areas; ~200,000 Americans visit areas of high risk each year; health issues for travelers are common; 20% of people who travel develop some illness while abroad, most minor; 50% of travelers who go to the tropics become ill; 0.2-0.5% of travelers become seriously ill and require hospitalization; ~25% of travelers leave within 2 weeks after they've made a decision to travel; a significant number of travelers don't know the language at their destination; one-third have no knowledge at all of local customs; <75% of travelers think of health issues related to travel and maybe one-third will prepare for specific issues in the countries that they're going to visit; the most common source of travel information is their primary physician; health information on travel booking websites is quite inaccurate; reliable and up-to-date information can be found at the Centers for Disease Control (CDC) website (cdc.gov/travel) or the World Health Organization (WHO) website (who.int/ith); the ministries of health of certain destination countries can be very helpful (eg, travelers going on the Hajj to Saudi Arabia can get very specific recommendations regarding things such as polio and meningococcal vaccines); commercial decision aids (eg, Shoreland's Travax) can be purchased and have very current, updated, and thorough information for travelers

Phases of travel health advice: pre-travel, during travel, and post-travel; pre-travel advice comprises general issues related to travel to any country; discussion of hygiene and sanitation issues, specific advice for each individual country, and personal issues related to individual health problems (eg, chronic diseases or medications may pose particular risks); a woman who is pregnant or planning to become pregnant has unique issues

Accidents: travelers have an increased rate of accidents compared with similar activities at home, and there's often increased morbidity and mortality; many countries do not have a well-defined 911 emergency system, so people may have greater problems receiving level 1 trauma care; emphasize the need for auto safety, avoiding alcohol and substances, and the need for seatbelts and helmets on motor scooters and bicycles; discuss the need for proper insurance, medical assistance, or medical evacuation coverage; many commercial insurance products do not have coverage outside the US; this includes Medicare; travelers with Medicare need to purchase a supplemental plan for when they are outside the US; travelers of any age need to have some sort of medical assistance or evacuation coverage to bring them home or to get them to an area of higher medical intensity if they have a serious health problem; medical assistance policies generally cost $1-$2/person/day and are recommended for people who will be traveling widely

Prescription medication: travelers need to take prescription medicines with them in their personal carry-on; have a list of generic or trade names of medicines so that if medicine is lost, stay is extended, or they run out of medicine, they can purchase more; in certain parts of the world (eg, Asia and Africa), counterfeit medications abound; advisable to take extra medication; carry medicine in the original pharmacy bottles; anyone traveling with needles or syringes should have a letter to attest that it is a legitimate medical need; have an extra pair of lenses or glasses and a copy of the prescription in case glasses are broken or contact lenses are lost; travelers with cardiac issues should take a copy of their EKG; know regulations for transport of controlled substances; some countries have restrictions on controlled substances; some stimulants used for ADD may not be allowed in certain countries

Jetlag: an issue for people going east or west; not a problem for those going south or north; jetlag is made worse by dehydration and fatigue; for the traveler going east, take melatonin 5-10 mg the day of travel at the destination bedtime and then continue that for 3 nights once destination is reached; for those going west, take melatonin at bedtime once they arrive

Motion sickness: can be a problem with all modes of travel; certain medications can be helpful; avoid neck and head motion; try to remain still; avoid closed, tight spaces with strong fragrances and odors; eat very lightly; transdermal scopolamine is effective as a preventive; it comes in a small patch worn behind the ear, and is applied 8-12 hours in advance; everybody gets dry mouth with scopolamine; some people are prone to drowsiness; it can't be prescribed to men who have prostatic hypertrophy or to women who have a bladder obstruction, and can't be used by anyone who has glaucoma; it's only available for adults or children over 12 y; must wash hands after applying to avoid dilation of pupils; antihistamines are also effective; diphenhydramine, dimenhydrinate (Dramamine), promethazine, and meclizine are somewhat effective; drowsiness is common with antihistamines

- Economy class syndrome: applies to all travelers; mostly related to the fact that airline seats are becoming narrower and people are feeling more cramped; mostly a problem for flights ≥10-12 hours in the air; risks of DVT are much greater in flights ≥8 hours; drink a glass of water or juice each hour and get up and walk around; this helps guarantee that traveler not simply sleeping for 10 hours in the air, which raises the risk of DVTs; compression stockings of 20-30 mm compression can help reduce DVT risk; avoid excessive alcohol or caffeine
- High altitude: the Andes, the Alps, the Himalayas, and the Rockies (areas >2500 to 3500 m elevation) present the greatest risk of altitude sickness (ie, acute mountain sickness, high altitude pulmonary edema, and high altitude cerebral edema); recommend 125 mg acetazolamide taken twice a day, starting 1 day prior to the ascent and continuing for 3 days at maximum altitude; people who have a predisposition to high altitude sickness are at much greater risk; mountaineers have a catchphrase to help avoid mountain sickness: climb high, sleep low; if you descend 100-200 m and sleep at that lower altitude, you're less likely to develop symptoms
- Traveling out of season: if traveling in winter time to the south, individual likely to be deconditioned and will have lost any of the suntan that they had during their own summer months; remind to acclimatize and be careful with exercise in hot, humid conditions; remind them to use sunblock and reapply after sweating and swimming
- Sexually transmitted diseases (STDs): much more common among travelers; have lower inhibitions and higher likelihood of high-risk behaviors; counsel to avoid high-risk behaviors or to at least protect themselves with condoms
- Hygiene and sanitation: untreated sewage and animal waste may contaminate food and drink; common forms of traveler's diarrhea are due to the coliform bacteria; simple rule is to cook it, peel it, boil it, or forget it; foods that are well cooked and steaming hot have a lower risk of transmission of traveler's diarrhea; fruits and vegetables that the traveler peels (eg, banana, orange) are much safer than a plate of fruit prepared in the kitchen; beverages that are bottled or boiled (eg, bottled water, bottled alcoholic or carbonated beverages, hot tea, coffee) are generally considered safe; ice cubes are not safe; many cases of traveler's diarrhea are self-limited; we don't recommend taking antibiotics as a preventive; if traveler has diarrhea, should hydrate well and use loperamide as long as there is no fever or bloody diarrhea; if symptoms persist, 1-3 days of azithromycin 250 mg is effective at curing most cases of traveler's diarrhea; anyone who remains ill for >3 days needs a medical diagnosis
- Type of traveler affects the advice you should give related to risks; business travelers, those going to visit friends and relatives (VFR travelers), and people going overland or trekking have very different risks than a family going on a holiday to visit a theme park
  - Business travelers: a challenge because often leave on very short notice; self-described experts; 60-80% as likely to use preventive measures against malaria as others; long-term business travelers file more claims for infectious disease and psychiatric illness
  - VFR travelers: make millions of trips every year; they bring back most of the malaria and a good deal of typhoid; in the UK, VFR travelers had 8 times the risk of developing hepatitis A; be aware that VFR travelers represent as much as 10% of the US population and give proper advice when traveler returns; when they lived in their country of origin, they may not have taken medication for malaria and may have developed some immunity; that immunity is gone within a few months of living in the US; eg, a graduate student who's been here for 1-2 years and returns home on holiday may be at much higher risk of developing malaria
- Destination-specific issues: risk assessment is based upon destination; is it a business center or a third-world destination? is it in the tropics? does the itinerary involve staying in a four-star hotel with screens and air-conditioned rooms or cabins/huts? consider personal health history (eg, underlying disease, medications, allergies, and age)
- Immunizations: most common vaccine-preventable disease for travelers is hepatitis A (occurs in 3,000 per million travelers); hepatitis B has a lower incidence (800 per million travelers); typhoid may be 30 per million travelers; asymptomatic polio may be only 20 cases per million travelers; symptomatic polio may be only 1 per million; very few countries require immunizations to enter; an exception is yellow fever; countries in sub-Saharan Africa, the Amazon region of South America, and some Asian countries have requirements for yellow fever vaccination; a single vaccination is good for a lifetime
- Malaria: most common insect-borne disease we worry about; >300 million cases worldwide per year with 2 million deaths; greatest risk is in VFR travelers; a variety of medications can be taken to protect against malaria; atovaquone-proguanil is the most common; taken daily, starting 1-2 days before entering the malarious region, and continued for ~1 week after leaving; doxycycline is taken daily but is continued for 4 weeks after leaving; mefloquine can be taken weekly, so it is less expensive than atovaquone-proguanil for long-term travel; it can be taken 1-2 weeks before leaving or with a 3-day loading dose, but is continued for 4 weeks after leaving; more neuropsychiatric side effects with mefloquine; people with a history of depression or trouble sleeping may have more difficulty with mefloquine; tafenoquine was approved in July 2018; not yet in pharmacies; a long-acting 8-aminoquinoline, which can be taken with a loading dose for 3 days and then once a week, and may turn out to be very effective; more convenient with fewer side effects; because it's an 8-aminoquinoline, must do G6PD testing, because those patients that are G6PD deficient will have severe hemolysis if they take tafenoquine; can also be taken as a so-called radical cure after exposure to *P. vivax* malaria; chloroquine can be used in certain restricted parts of the world (eg, Mexico, Haiti, Central America, the Middle East); taken once a week and continued for 4 weeks after leaving
- Preventive measures: wearing long-sleeved shirts and long pants, using plenty of repellant with polymer-based DEET or picaridin on the skin, 0.5% permethrin

can be impregnated into clothing, netting, and tents); combination of DEET on the skin and permethrin on clothing has been found to reduce mosquito bites by ~99.9%; pyrethrin knockdown sprays can be used; nothing works all the time, so need to know the symptoms of malaria and other insect-borne diseases such as leishmaniasis and Lyme disease

DEET: there's an urban legend that DEET can be a dangerous drug; since 1957, it's been estimated that there are over 10 billion uses of DEET; between 1961 and 2000, there were a total of 42 published cases of reactions to DEET; the EPA re-registered DEET in 1980 with a risk of 1 per 100 million adverse events; it is not oncogenic, teratogenic, or uniquely toxic to children; it is toxic if ingested, however, so keep away from young children; given the risks of malaria and other insect-borne diseases, we strongly recommend the use of DEET; other repellants (eg, picaridin, oil of eucalyptus) are also effective; eucalyptus is less effective than DEET; picaridin protects about as well as DEET, and is not as oily or greasy, and it's not a plasticizer; some concern about the interaction between DEET and sunscreen; the interaction does not affect the effectiveness of DEET, but it may decrease the effectiveness of the sunscreen; the recommendation is to put the sunscreen on first, let it dry, and then apply DEET

Development of malaria after travel: if travelers have been to a part of the world that has malaria, any fever or flu-like illness in the first few weeks/months after returning from a malaria zone is malaria until proven otherwise; patients who develop fever or flu-like illness after they traveled to an area with malaria need an urgent referral to a facility that can perform a malaria RDT (rapid diagnostic test) or blood smear; each year, a few American travelers die from malaria because they fail to take appropriate medication or recognize early symptoms as being compatible with malaria

Water-borne diseases: parasitic diseases (eg, *Giardia*, *Cyclospora*, *Cryptosporidia*, amoebiasis, and *Angiostrongylus* — rat lungworm) are very rare in short-term travelers; schistosomiasis can be contracted by swimming in areas of freshwater where snails are present, particularly in parts of Africa; we encourage people to stay out of freshwater

Special considerations for diabetic travelers: travelers need to make adjustments if they're going across time zones; they may have to adjust their insulin or their oral agents; if traveling with needles, they'll need a letter certifying that there's medical need; explore whether injectables require refrigeration or can be kept at room temperature; if they're going to a tropical area, they need to be protected from areas of high heat and high humidity; ensure your traveler has backup batteries or power supplies for blood glucose meters or insulin pumps

Other special considerations for patients: those taking H2 blockers or pump inhibitors, those with GERD, ulcers, or gastritis may be at higher risk of traveler's infection, diarrhea, and enteric infections because pump inhibitors reduce acidity, which is a prime means of protection for these infections; women who are pregnant or may become pregnant cannot take sulfa, quinolones, or tetracyclines; they may have unique problems with certain anti-malarials; current CDC advice is that couples who have had potential Zika exposure should use condoms or abstain for 2 months after the woman has been exposed and 3 months after the man has been exposed; traveling with children creates a whole range of separate issues, including palatability of anti-malarials; avoid quinolones or tetracyclines, but short courses of doxycycline are acceptable for children

Special considerations for immunocompromised travelers: the following travelers are not immunocompromised: those who completed chemotherapy >3 months ago, people on low-dose or alternate-day steroid therapy, those taking topical steroids (unless prolonged or extensive), those who received intra-articular steroids, those on antibiotics, or those with a low-grade febrile illness or mild URI; there are more and more travelers who've had solid organ transplants; study showed 36% of solid organ transplant recipients traveled outside Canada or the US; many were VFR travelers and/or visited tropical countries; almost 90% were taking 2+ immunosuppressive drugs; many received pre-travel advice from their transplant specialist, who was often not well-informed about travel medicine; 63% of these travelers went to areas endemic for hepatitis A but only 5% received immunization

Ticks and Tick-borne Diseases

Ticks: the *Tick Management Handbook* is available online, published by the Connecticut Agricultural Experiment Station (ct.gov/caes); contains information on ticks and tick-borne infections and specific recommendations for property owners about safe landscaping recommendations

Tick families: two major families, the hard and soft ticks; hard ticks include ticks in the *Ixodes* family; soft ticks are members of the *Argasid* family; *Ixodes scapularis* (black-legged or deer tick) is found in the northeastern, southeastern, and to some degree mid-western US; *Ixodes pacificus* is found in northern California and the upper part of the West Coast; *Amblyomma americanum* (lone star tick) is found in the southeastern US; American dog tick (*Dermacenter variabilis*) does not transmit any of the diseases to be discussed; the only relevant soft tick in the eastern US is a bat tick, which is rarely seen because it does not tend to bite humans; in the western US, the *Ornithodoros* ticks are found in the Rockies and can transmit relapsing fever; ticks can expand 5-10 times their initial size after feeding; ticks are stealth feeders; if they are left alone, they stay intact for 7-10 days while feeding; the longer they feed, the bigger they can get

Lyme disease: the most common tick-borne infection; found in the northeastern US and the upper Midwest; range is spreading and is now found in northern Maine and southern provinces of Canada, in Quebec and Ontario, where it was never found before; *Ixodes* ticks are found worldwide, including northern and western Europe and southern Russia to the Pacific Ocean, and Lyme disease is found in those regions; ticks transmit more than Lyme disease; transmit *Babesia*, causing babesiosis, which was first identified in humans in 1957; they carry viruses (eg, tick-borne encephalitis, which is found in Europe, and Powassan virus or deer tick virus, which is found in the US); anaplasmosis, which used to be called ehrlichiosis, is caused by the bacterium *Anaplasma phagocytophilum* and was first identified in 1994; *Ehrlichia muris* can cause infection; Lyme disease is caused by *Borrelia burgdorferi*

(newer strains are *Borrelia miyamotoi* and *Borrelia mayonii*, identified in the last 10-15 years)

Life cycle: 4 stages; eggs are laid in winter and tend to hatch in the late summer into larvae; they molt into nymphs, which are present in the spring; nymphs molt into adults, which are found in the autumn and can overwinter; larval ticks, which are found in the late summer, are uninfected with Lyme disease; nymphs that have been feeding on infected rodents are more likely to transmit Lyme disease to humans; nymphal ticks are predominant vector for Lyme; most biting occurs in the mid/late spring/early summer, that is peak incidence of Lyme disease; ticks can bite year-round; ticks don't hibernate; they become less active in cold weather, but if the weather warms up in the winter, the adult ticks are still present and can bite and transmit infection

Tick-borne infections: incidences of Babesia, Lyme, and Anaplasma have been dramatically increasing over the last 15 years; the ecological range is spreading and the absolute numbers of cases are increasing; Lyme has a peak in ages 5-10 and 40-50; endemic areas with outdoor activities pose the greatest risk for Lyme acquisition; ticks must be attached for 2-3 days before they can transmit Lyme; Babesia and Anaplasma can be transmitted within the first few hours of feeding; typically see ~2-4 cases of Babesia or Anaplasma for every 100 cases of Lyme; Babesia is a much greater risk for the very young and the very elderly, people who have no spleen, and people who are immunocompromised; Babesia can be transmitted both congenitally and in transfusion, and case fatality can be as high as 25%; Anaplasma also can be a fatal disease with both liver and kidney failure, and can also be transmitted by transfusion

Lyme disease: most common symptom of Lyme disease is characteristic rash, which has been called the bull's-eye rash (but often does not look like bulls's-eye)- a large erythematous plaque that expands;; usually comes 1-2 weeks after the tick bite; people who are not diagnosed early can develop later stages of Lyme with symptoms of arthritis, Bell's palsy, radiculoneuropathy, or neurological Lyme with meningitis; there is an endocarditis, a myocarditis that can be caused by Lyme, which is mostly notable for conduction system disease with very slow pulse and heart block; symptoms generally improve rapidly after treatment; cardiac Lyme patients are monitored in ICU with a temporary pacemaker, but it is very rare for anyone to require permanent pacing after treatment

Borrelia: forms of Borrelia infection in Europe tend to have slightly different manifestations with more skin and lymphocytoma manifestations; erythema migrans can be vesicular or necrotic; not unusual for people to come in with nasty-looking reddish lesion, believing that they've been bitten by a spider

STARI (southern tick-associated rash illness): mostly in the Southeastern US; associated with the *Amblyomma americanum* (lone star tick); looks like a Borrelia or rickettsial infection, but no pathogen has been identified; patients have an erythema migrans-like rash, fever, headache, and myalgias; respond quickly to doxycycline; *Amblyomma americanum* has a big white spot on the back, and are much more aggressive biters; patients with STARI are much more likely to recall being bitten by a tick than Lyme disease patients; less likely to have multiple skin lesions and generally recover more rapidly than Lyme disease

Diagnostic testing for Lyme: based upon an ELISA (enzyme-linked immunosorbent assay) test, which, if negative, does not warrant any further testing; if the ELISA is positive, the CDC recommends doing a western blot test; IgM will generally show up within 1-2 weeks of illness and if 2/3 IgM bands are positive, that's considered a positive western blot for current or recent infection; IgG antibodies generally show up a few months later; if the individual has ≥5/10 positive IgG bands, that is considered evidence of a prior or resolving infection with Lyme; other non-standardized, non-FDA-approved tests exist but should not be relied upon; ~25% of patients with Lyme may have musculoskeletal symptoms, which can last for a few months; up to 10% of patients with Lyme arthritis may develop a chronic synovitis that doesn't respond to antibiotics; a small minority of patients develop post-Lyme disease syndrome with subjective symptoms that don't respond to antibiotics; there's controversy about this (eg, serologic testing doesn't really prove infection)

Lyme treatment: 2 weeks of doxycycline 100 mg twice a day, is thought to be highly effective, but antibiotics may only eliminate viable spirochetes; there may still be inflammatory products that take time to clear, and there may be some objective signs due to residual damage or underlying genetic susceptibilities associated with immune dysregulation; no evidence that active infection with *Borrelia* can persist after recommended treatments; in Lyme-endemic areas, people with new episodes of erythema migrans probably are having reinfection rather than recrudescence of a partially treated infection; in a large European study, patients received 2 weeks of IV ceftriaxone and were randomized to doxycycline, clarithromycin, or hydroxychloroquine; no differences between antibiotic treatment groups and those receiving placebo after IV ceftriaxone, but nearly two-thirds had at least 1 drug-related adverse reaction; supports recommendation to restrict the use of long-term antibiotics in patients with vague symptoms, which may not be due to active infection

Clinical pearl: Lyme serology cannot be used to follow up on response to therapy, because it may remain positive for months or years, and serology can't be used to prove eradication of the *Borrelia* organisms; patients with "treatment-resistant Lyme disease" may have fatigue, memory problems, myalgias, and arthralgias; unclear whether this is a chronic infection, a persistent inflammatory response, or an autoimmune reaction to living or dead spirochetes

Borrelia miyamotoi: an interesting pathogen because it is related to the so-called relapsing fever spirochetes (usually found in the soft body ticks), but this is found in *Ixodes* (hard body ticks); first found in 1995 in Japan; first human cases were identified in 2011 when they were published as a series of patients from Russia; first US cases published in 2013; *B. miyamotoi* is widespread wherever Lyme disease is found, but in much lower frequency (1%-4% of ticks carry *miyamotoi* vs *burgdorferi*); *miyamotoi* seems to be fully cured with the same doxycycline 2-week regimen as Lyme disease; *miyamotoi* can be transmitted by larval ticks, so may see cases in late summer (July, August, September); appears

to be transmissible within 24 hours of feeding; patients may not test positive with the standard Lyme disease test, so may require specialized testing

Borrelia mayonii: was detected in the last few years in Minnesota, Wisconsin, and North Dakota; patients may have more nausea, vomiting, and atypical rash; some patients have been hospitalized and spirochetes have been found in the blood, which is very unusual for Lyme

Human granulocytic anaplasmosis: caused by *Anaplasma phagocytophilum*; symptoms usually begin 1-2 weeks after the bite of an infected tick; symptoms are fever, headache, muscle pain, malaise, and nondescript systemic symptoms; can be fatal if not treated properly; case fatality rate is ~1%; continue doxycycline for ~3 days after fever subsides

Powassan/deer tick virus (*flavivirus*): produces encephalitis, but is very rare (<100 cases reported); no prevention other than prevention of tick bites with repellants

Babesia: closely related to malaria, but transmitted by *Ixodes* ticks; found in red blood cells; treatment is atovaquone-azithromycin or clindamycin and quinine; found worldwide and occurs in the same places as the ticks that carry Lyme disease; patients who are asplenic or elderly have more severe disease; 1-2% of blood donors are found to be seropositive, so in some parts of New England, the blood supply is being screened to avoid transfusion-related cases; although some patients with tick-borne infections may have positive serology, *Babesia* can be self-cured in a healthy person; if patient has symptoms and positive serology, do a smear to look for parasite presence; a positive serology without any parasites present in the blood smear probably does not require treatment, especially if the patient is not having symptoms

Tick bite and red meat allergy: syndrome found in parts of the US where the lone star tick is present; alpha-galactose (a carbohydrate) is in tick saliva and red meat; people who've been bitten by *Amblyomma* ticks may develop an allergy to this carbohydrate in the tick saliva; if they eat red meat, they can develop urticaria, itching, hives, and rarely, life-threatening anaphylaxis; disease will spread, as the *Amblyomma* tick is moving northward; in the last 5 years, more *Amblyomma* ticks are being found in the northeastern US; be aware that certain cases of chronic or acute urticaria or hives may be related to this tick bite red meat allergy

Clinical pearl: if you're in a part of the country that has *Ixodes* ticks, anyone who presents with fever and flu-like symptoms from April to October may have a tick-borne infection and should be tested; depending on how sick they are, you can start presumptive treatment with doxycycline 100 mg twice a day; ticks can carry multiple pathogens, so even if a patient has an erythema migrans rash, they could still be infected with *Babesia* or *Anaplasma*; recommend a CBC, a blood smear for *Babesia*, and a Lyme ELISA with the reflex to the western blot; if your patient has leukopenia and thrombocytopenia, a white count of 1500, and 80,000 platelets, it's highly suggestive of Lyme or *Anaplasma*; when patients are treated and shown to be infected, they have a dramatic clinical response; if you give a patient doxycycline in this setting and within 24 to 48 hours they've defervesced and feel terrific, even if you don't get a positive serology or a positive smear, you can be fairly sure that you've treated a tick-borne infection; for complex cases, possible to order special testing from specialized laboratories for *Borrelia miyamotoi* and PCR analysis for DNA presence

How to treat a person who says they've been bitten by a tick: good evidence that doxycycline 200 mg for adults over the age of 18 reduces the risk of Lyme by about 87% if treated within 3 days of the tick bite; note, however, that only 3% of patients studied did have Lyme infection; note also that stat dose of doxycycline doesn't protect against *Babesia* or *Anaplasma*; many patients will bring in a tick asking to have it tested; lecturer argues against this, as testing is hard to get, takes several weeks, and sis not clinically useful

Personal protection: long-sleeved shirts, long pants, repellants with polymer-based DEET or picaridin on the skin, and 0.5% permethrin on clothing, netting, or tents; if you create a barrier of ~3 feet of woodchips between your yard and the woods, it dramatically reduces the likelihood that ticks or small rodents will be present near your home, which helps to reduce the risk of tick-borne infection

Suggested Reading

Mahadevan SV et al: Preparing for international travel and global medical care. *Emerg Med Clin North Am* 2017 May;35(2):465-84; **Ranque-Garnier S et al:** Management of patients presenting with generalized musculoskeletal pain and a suspicion of Lyme disease. *Med Mal Infect* 2019 Feb 11. doi: 10.1016/j.medmal.2019.01.008. [Epub ahead of print]; **Tan EM et al:** Impact of pre-travel consultation on clinical management and outcomes of travelers' diarrhea: a retrospective cohort study. *Trop Dis Travel Med Vaccines* 2018 Dec;4:16; **Wormser GP et al:** Borrelia miyamotoi: an emerging tick-borne pathogen. *Am J Med* 2019 Feb;132(2):136-7.

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Skin and Soft Tissue Infections; Osteomyelitis; CNS Infections

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Skin and soft tissue infections: in the US, the 3 most common are cellulitis, boils (furuncles), and surgical site infections; these can often be managed in the outpatient setting if appropriate follow-up is arranged

Cellulitis: common in all age groups; can be seen in young, healthy, active people because cuts and scrapes that occur during sports and other activities can become infected; cellulitis is also common in older people, especially if they have preexisting edema (eg, leg edema), which may be due to a sedentary lifestyle, congestive heart failure, renal insufficiency, or other reasons; cellulitis is an acute bacterial infection of the dermis of the skin, characterized by an intense inflammatory response; clinically, cellulitis presents as a painful, red, warm area of the skin, in which contiguous areas of the skin are involved; lymphangitic spread may occur, especially when the cellulitis is due to streptococcus; although cellulitis is painful, especially when touched or squeezed, the patient can usually obtain some comfort by elevating the affected area and immobilizing that part of the body; inordinate or excruciating pain despite the above postural adjustments is a clue that the patient may have something more serious than cellulitis (eg, necrotizing fasciitis, gas gangrene, or other)

Imaging: clinicians are often reluctant to make the diagnosis of cellulitis without imaging; however, *imaging is not required* for ordinary, uncomplicated cellulitis; cellulitis is a bedside clinical diagnosis, not a radiological diagnosis; ordinary x-rays are usually not helpful because they will only show swelling of the skin and soft tissues, which is already evident from the physical exam;

"Chronic cellulitis": there is no such thing as chronic cellulitis, despite the frequency with which this term is used in medical charts; it is possible for patients to have recurrent cellulitis, especially if they have lymphedema in an extremity (eg, chronic swelling of the legs or arm lymphedema following mastectomy)

Treatment: cellulitis is caused by a very narrow spectrum of bacteria, namely *Staphylococcus aureus* and beta-hemolytic streptococcus; gram-negative bacteria (eg, *E coli* or Pseudomonas) do not cause cellulitis; broad-spectrum antibiotics directed against gram-negative organisms (eg, piperacillin, tazobactam, aztreonam, cefepime) are not needed and are not recommended for cellulitis; IV antibiotics with good activity against the pathogens that cause cellulitis include vancomycin, cefazolin, and nafcillin; clindamycin is also commonly used, but its activity against *S aureus* is slipping in the US (in lecturer's hospital, about 40% of *S aureus* strains are resistant to clindamycin); beta-hemolytic streptococcus are also showing increased resistance to clindamycin in the US; oral antibiotics with good activity against cellulitis include cephalexin, dicloxacillin, and amoxicillin clavulanate; clindamycin is also available orally, but is subject to the same caveats as the IV form; macrolide antibiotics (eg, erythromycin and azithromycin) are commonly used for treating skin and soft tissue infections, but are not recommended; *S aureus* and beta-hemolytic strep both have fairly high levels of resistance to the macrolide antibiotics; consider moxifloxacin as an alternative in a patient with multiple antibiotic allergies

Boils (furuncles): *S aureus* is the pathogen involved in the vast majority; if examination reveals pustules on the skin, these should be cultured for pathogen identification and susceptibility; the number of community-acquired methicillin-resistant *S aureus* (CA-MRSA) cases exploded in the early 2000s; the numbers have since stabilized, but methicillin resistance is still seen frequently in outpatient clinics, urgent care centers, and emergency rooms; methicillin-resistant strains no longer predominate, so we see a mixture of methicillin-sensitive (MSSA) and methicillin-resistant *S aureus* (MRSA) strains causing skin infections in our populations; boils should be treated by incision and drainage; small lesions (1-1.5 cm in diameter or smaller) may be drained by needle aspiration; any pus obtained should be sent for microbial culture, because results will inform options for antibiotic therapy; if the patient has MRSA, he/she could be sent home on oral trimethoprim-sulfa, doxycycline, or linezolid; if the patient has MSSA, then cephalexin or dicloxacillin would be better options, assuming the patient is not allergic; patients whose medical records state that they are allergic to penicillin should be carefully questioned about the nature of their allergy; they should be asked if they have ever been treated with a cephalosporin (eg, cephalexin or cefuroxime) because many have been treated uneventfully with cephalosporins, making it unnecessary to do allergy skin testing; electronic medical records can also be searched, selecting all visits to see if the patient has previously been prescribed and has tolerated cephalosporins or penicillins

Surgical site infections (SSIs): now reportable as part of quality measures in the US; common to see SSIs labeled as "cellulitis," but be aware that this diagnosis

is often used by operating surgeons to reduce their rates of postoperative complications; the distinction between SSIs and ordinary cellulitis is important, however, because postoperative SSIs have a broader spectrum of possible pathogens than pure cellulitis, and different pathogens may be suspected depending on surgical site; for example, postoperative SSIs in the abdomen or pelvis may frequently be caused by gram-negative bacteria; anaerobic bacteria may also be involved in surgical sites in the abdomen, pelvis, or in operations on the groin or axilla; enterococci may also be pathogens in SSIs; enterococci are not covered by cefazolin, which is commonly given as the preoperative antibiotic for surgical operations

Rarer, but more serious, potentially life-threatening, soft tissue infections: require hospital admission, emergent consultation with surgery and/or infectious disease specialists

Necrotizing fasciitis: an uncommon but life-threatening infection, which can be difficult to recognize in its early stages; most commonly seen in the extremities, but the trunk, buttocks, and abdomen can also be involved; inordinate pain out of proportion to physical findings should be a clue that something other than cellulitis might be going on and that further investigation is required; onset of sepsis or septic shock is another clue that the patient may have an infection far more complicated than cellulitis; another clue is a high white count, especially if it is accompanied by a high percentage of band forms;

Diagnosis: in contrast to cellulitis, imaging is mandatory in cases where necrotizing fasciitis is suspected; ordinary x-rays useless; proceed directly to CT scan, or in some cases, MRI scan if it will not cause too much of a delay in the evaluation; MRI scans take longer to complete than CT scans, and patients with necrotizing fasciitis are often in a great deal of pain and cannot hold still in the MRI scanner long enough for good images to be obtained; physical findings may first appear as areas of numbness on the skin overlying the affected area; dark discoloration of the skin, or the appearance of dark or purple/black bullae or blisters are clues that something bad is happening in the deep tissues; if blisters or bullae appear, they should be aspirated with a needle after cleaning the skin with an alcohol wipe and the blister fluid sent for culture; blister fluid from intact blisters is normally sterile, so microbes that grow from the blister fluid of an intact blister should be taken seriously;

Treatment, emergent: complete surgical debridement is usually required to save the patient's life, so surgery should be contacted immediately; infectious diseases consultation may also be appropriate, but taking the patient to the operating room should not be delayed solely for the purpose of obtaining a second opinion from the infectious diseases consultant;

Typology of necrotizing fasciitis: infected fluid found at the time of surgery is often described as dirty dishwater with a gray or brownish color, and not actual pus; in patients who have not been exposed to unusual environments, such as salt or brackish water, the microbial etiology of necrotizing fasciitis usually falls into 2 types; type 1 necrotizing fasciitis is polymicrobial (ie, due to a mixture of pathogens, generally gram-negative rods, anaerobes, and sometimes gram-positive organisms as well); in type 1 necrotizing fasciitis, the microbial cultures might grow *E coli*, *Bacteroides*, and *Peptostreptococcus* (an anaerobic streptococcus); type 2 necrotizing fasciitis is monomicrobial, usually due to group A streptococcus; this type of streptococcal infection has been commonly referred to as "flesh-eating disease;" recently, cases of necrotizing fasciitis due to CA-MRSA alone have also been described;

Treatment, antibiotic: until the microbiology results are known, broad and aggressive antibiotic coverage is appropriate, often with a regimen such as IV vancomycin plus IV piperacillin-tazobactam (Zosyn), or vancomycin plus meropenem; in some cases, an aminoglycoside or metronidazole might be added; patients who develop necrotizing fasciitis after exposure to saltwater or to brackish water might have infection due to *Vibrio vulnificus* or *Vibrio alginolyticus*; infections due to noncholera vibrios are often seen in patients with underlying liver disease (eg, compensated cirrhosis or a history of hepatitis C); most common in southern states, especially those bordering the Gulf of Mexico; can be encountered elsewhere in the summer months when the water is warm; because vibrios are not susceptible to penicillins, patients must be treated with a double or triple combination of antibiotics (eg, IV doxycycline plus IV ceftriaxone or another third-generation cephalosporin), sometimes with an aminoglycoside added as a third drug; *Aeromonas*, an organism that thrives in fresh water, can also cause necrotizing fasciitis after injuries in water; antibiotic treatment does not need to be unnecessarily prolonged; if the patient receives prompt surgery, you can usually tell by day 10 whether he/she is going to survive; duration of antibiotics may be as short as 10 to 14 days, as long as the patient has had adequate surgical debridement;

Variants of necrotizing fasciitis described and named historically: Fournier's gangrene is a type of necrotizing fasciitis involving the scrotum and perineum in men, or the vulva and perineum in women; other terms include synergistic necrotizing cellulitis or progressive bacterial synergistic gangrene; it is more important to obtain accurate microbiology on these patients than to try to figure out which of these quaint and somewhat antiquated names to apply to their condition

Osteomyelitis: will deal primarily with adults; in children, often hematogenous, with a better prognosis than in adults, due to good blood supply in the bones of children; acute hematogenous osteomyelitis often presents in toddler-aged children who begin limping; x-ray shows a lytic lesion in the shaft of the long bone, often near the metaphysis; *S aureus* is the number one pathogen in osteomyelitis in children and adults;

Osteomyelitis in adults: the vast majority of cases of are chronic osteomyelitis, the definition of which is somewhat vague and depends not just on the duration of illness, the onset of which may be difficult to determine; more important whether there is formation of necrotic devitalized bone, such as sequestrum; sequestrum is dead pieces of bone that are detached and separated from the rest of the viable bone;

although formation of sequestrum usually takes weeks to occur, it can occur more quickly (eg, after a compound comminuted fracture or in a setting of a prosthetic device); necrosis of bone is thought to occur due to increased intramedullary pressure in the bone marrow in the setting of infection, causing vascular insufficiency; often, you cannot tell whether the patient has acute or chronic osteomyelitis: should treat the patient as if they have chronic osteomyelitis; the Cierny-Mader staging system is applied to long bones; system is based on the affected portion of the bone, the condition of the bone, and the presence of compromising factors in the host; in US adults, most cases of osteomyelitis occur in people with diabetes and peripheral neuropathy, or in people with peripheral arterial disease

Imaging modalities: best modality is a question of active discussion; nuclear medicine bone scans, which now mostly use technetium-99 as the isotope, are quite sensitive (>90% for detecting osteomyelitis), but lack specificity; any disease or condition that causes remodeling of bone will usually cause uptake of the technetium-99 tracer (eg, recent fractures, osteomyelitis that has been successfully treated, Charcot arthropathy, osteoporosis with stress fractures, arthritis, cancer with bone metastases); the specificity of the nuclear medicine bone scan in the past was about 60%, but more recent reports indicate that it may be as low as 30%; the nuclear medicine bone scan is most helpful if it is negative, but this does not usually happen; probably significant that centers with greatest expertise in osteomyelitis order fewest bone scans; plain x-rays can be used to evaluate for osteomyelitis, especially if the infection has been going on for more than 2 to 3 weeks; before that time, it is unlikely that a plain radiograph will show bony changes; MRI is the imaging modality that has the greatest combination of sensitivity and specificity, with >90% sensitivity and specificity when interpreted by an expert; the bedside exam can also help you determine your index of suspicion for osteomyelitis; if bone is visible or palpable at the base of a wound, then your suspicion for osteomyelitis should be high, even if the imaging tests are inconclusive

Microbiological diagnosis:

Bone biopsy: often recommended to determine microbial etiology; in lecturer's center, however, orthopedic and general surgeons are very reluctant to perform a bone biopsy through an infected wound and into a bone that appears intact on x-ray, reasoning that if the patient did not have osteomyelitis before the procedure, then they will have it after the procedure because of introduction of contaminated material and microbes into the bone tissue from the overlying wound infection; bone biopsy is best if it can be performed through intact, uninfected skin (eg, needle biopsy of septic discitis or vertebral osteomyelitis to obtain material for culture and histopathology);

Indications for surgery: if the patient has changes on x-ray showing a moth-eaten appearance of the bone or the formation of sequestrum, surgery is mandatory for therapy, not only for diagnosis; another complication of chronic osteomyelitis is the formation of involucrum (a bony sheath that can form around the area of infection); sequestrum and involucrum must both be removed if you wish to cure the patient, and moth-eaten cortical bone should also be debrided away to give the greatest chance for cure; if the patient requires surgery, microbial cultures and histopathology should be sent from the operating room;

Microbial diagnosis: blood cultures can be valuable, especially in cases of known or suspected vertebral osteomyelitis, where patients are frequently bacteremic; the most common microbial cause in children and adults and in both acute and chronic disease is *S aureus*; this does not tell you whether the patient has MRSA or MSSA, an important piece of information for the selection of therapy; other microbial causes of osteomyelitis include beta-hemolytic streptococcus, gram-negative pathogens (eg, *E coli* or pseudomonas), candida yeasts, and occasionally other less common pathogens; *Propionibacterium acnes* is also an occasional cause of osteomyelitis, sometimes even in the absence of a shoulder prosthesis; tuberculosis can also cause osteomyelitis; TB of spine called Pott's disease; microbial cultures for acid-fast bacilli may be indicated in an appropriate setting

Therapy: depends on the microbial etiology; if there is no microbial pathogen identified, even from superficial wound or blood culture, it is my practice not to embark on a long course of IV antibiotics; usually try to devise some type of oral regimen; for MSSA, an antistaphylococcal penicillin (eg, nafcillin or oxacillin) or a first-generation cephalosporin (eg, IV cefazolin) is usually recommended; for MRSA, IV vancomycin is usually the first choice; if the patient cannot tolerate vancomycin due to renal toxicity or rash, alternative antibiotics include the newer cephalosporin ceftaroline, which has anti-MRSA activity, or IV daptomycin; linezolid is an option, but it causes thrombocytopenia that becomes progressively worse the longer the drug is continued; most patients, especially the elderly, cannot tolerate linezolid more than about 4 weeks before thrombocytopenia becomes so severe that the drug must be stopped; linezolid also interacts with serotonin-selective reuptake inhibitors (SSRIs), commonly prescribed as antidepressants; coadministration of linezolid and SSRIs is generally contraindicated;

Newer antibiotics: the new, longer-acting lipoglycopeptides, oritavancin and dalbavancin, are also being tested, although they are not FDA-approved for this indication; the advantage of these drugs is that they last approximately 2 weeks in the human body, so they may be useful to complete therapy in someone who is not a good candidate for home IV antibiotic administration; these drugs are quite expensive and the hospital is not reimbursed for the extra cost if the antibiotic is given to inpatients

Gram-negative osteomyelitis: therapy is more difficult to prescribe because of the rise of multidrug-resistant gram-negative pathogens (eg, carbapenem-resistant enterobacteriaceae (CRE), drug-resistant pseudomonas); necessary to be guided by the pathogen's antibiotic susceptibility report; commonly considered antibiotics include IV cefepime, IV ceftazidime, ciprofloxacin, or levofloxacin; because quinolones are well absorbed from the GI tract, they can be administered orally and generally do not require home IV therapy;

Duration of therapy for osteomyelitis: usually given as 6 weeks, but there is no guarantee that a patient will be cured at the end of therapy, especially if they did not receive adequate surgical debridement at the beginning of their antibiotic course; another common reason for antibiotic failure is failure to remove infected prosthetic material at the infection site; most clinicians check the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) on a weekly or biweekly basis during therapy to see if there is an adequate response to the administered antibiotic; if there has been no decrease in the ESR or the CRP by the third or fourth week of IV antibiotics, it is time to stop, reevaluate, and possibly ask for repeat surgical debridement;

IV vs oral treatment: common fallacy is that treatment of osteomyelitis must always include IV antibiotics; IV antibiotics are used for many patients because many have drug-resistant pathogens for which good oral antibiotic therapy is not available, requiring use of IV antibiotics (eg, vancomycin, piperacillin, tazobactam, cefepime, or carbapenems); in an article by Spellberg and Lipsky in *Clinal Infectious Diseases* (2012) reviewing studies of antibiotic treatment for osteomyelitis, oral antibiotics (trimethoprim-sulfa, doxycycline, clindamycin, and quinolones) generally performed similarly to IV antibiotics; this article also noted that cure rates for osteomyelitis due to pathogens other than pseudomonas were the 60 to 90% range with IV therapy; for osteomyelitis due to *Pseudomonas aeruginosa*, the cure rate was only about 50%, which is unacceptably poor; one should be careful about giving a patient overly optimistic assurance about their chances of cure from a course of therapy, even with 6 weeks of IV antibiotics;

Special anatomic cases:

Vertebral osteomyelitis: special form of osteomyelitis; blood cultures are positive in ≈50% of cases; positive blood cultures provide an important clue as to what drugs could be used for treatment; often, patients have pain or collapse of vertebral bodies or other structural complications which require surgery; if the degree of vertebral body collapse is small, however, medical treatment alone might be sufficient; vertebral osteomyelitis frequently accompanied by septic discitis of the adjacent disc;

Osteomyelitis of the mandible: another special case, with a better prognosis than at other sites because of the good blood supply to the jaw and the face; determining a microbial etiology is important; often, patients with osteomyelitis of the jaw require operative intervention, whether to reset the jaw using metallic wires, to rule out cancer, or to remove infected teeth; when oral surgeons operate, microbial cultures should be sent if osteomyelitis is observed or suspected

Empiric regimens of IV antibiotics for osteomyelitis: when there is no known microbial etiology, selection of IV antibiotics is quite difficult; I usually recommend an oral antibiotic or an oral antibiotic combination; if you decide you absolutely must administer IV antibiotics for a patient with no microbiology to guide you, then IV vancomycin plus another antibiotic with activity against gram-negative organisms would be recommended; this should only be done rarely and reluctantly

CNS Infections: bacterial infections generally fall into 2 categories: 1) meningitis, and 2) other intracranial infections (eg, brain abscesses and subdural empyema)

Bacterial meningitis vaccines: community-acquired bacterial meningitis has become quite a rare illness in the US due to the availability of highly effective vaccines

Haemophilus influenzae B vaccine (HIB): one of the first vaccines in which a polysaccharide was conjugated to a carrier protein to improve immunogenicity; this vaccine first appeared in the 1980s and drastically decreased the number of cases of meningitis due to that pathogen, which was primarily seen in children less than 3 years of age

Pneumococcal conjugate vaccine: first version called PCV7 or Prevnar; a conjugate vaccine in which the streptococcal carbohydrate antigen is linked to a protein carrier; current version of this vaccine, Prevnar 13, is a 13-valent vaccine; vaccine initially licensed for children; now licensed and used in adults; should be the first pneumococcal vaccine given to older adults before the pneumococcal polysaccharide vaccine (Pneumovax), a 23-valent carbohydrate-only vaccine

Menactra and Menveo: quadrivalent vaccines against *Neisseria meningitidis* with activity against 4 serotypes (A, C, Y, and W135); a separate vaccine against meningococcus type B is now also available

Bacterial meningitis pathogens: the few cases of community-acquired bacterial meningitis that we do see are caused by less common pathogens such as beta-hemolytic streptococcus, alpha streptococcus, pneumococcal serotypes not covered by the vaccine, *Listeria monocytogenes*, and a smattering of other pathogens; many cases that we see are caused by spread from a nearby infectious focus (eg, bacterial sinusitis, otitis media, infected teeth, or infections resulting from IV drug use)

Signs and symptoms: because of the current relative rarity of bacterial meningitis and clinicians' unfamiliarity with the disease, many patients who are hospitalized with bacterial meningitis have been seen by many healthcare providers prior to their admission to the hospital and have often received a course or several courses of antibiotics prior to admission, often antibiotics that are not considered effective for meningitis; when a patient with bacterial meningitis presents to the hospital, a lumbar puncture should be performed promptly, followed by antibiotics; the recommended antibiotic regimen is vancomycin plus either ceftriaxone or cefotaxime; adjunctive steroid administration is effective only if given prior to or at the same time as the first dose of parenteral antibiotics; clinicians at lecturer's center do not often initiate steroid therapy, because many patients have been seen in outlying hospitals and have previously received a dose of IV antibiotics

Brain abscess: a serious infection of the brain parenchyma; patients with brain abscess only have fever about 50% of the time; present with headache, focal neurologic signs, or seizures; usually diagnosed when someone orders neuroimaging on a patient with these symptoms; brain abscesses appear as space-occupying lesions,

usually in the cerebral cortex or the cerebellum; when intravenous contrast is used, brain abscesses show a rim of enhancement and usually show a great deal of edema in the surrounding brain tissue; appearance of the head CT or the brain MRI can be mimicked by other conditions (eg, CNS toxoplasmosis in patients immunocompromised by AIDS or immunosuppressive medications); brain tumors also frequently present with seizure and ring-enhancing brain lesions;

Diagnosis: obtaining tissue for histopathology is vital, along with appropriate microbial cultures; culturing for mycobacteria, fungi, and nocardia may be needed in addition to aerobic and anaerobic bacterial cultures; neuroimaging may also reveal other findings (eg, sinusitis or mastoiditis), which may provide clues to the microbial etiology of the brain abscess; brain abscess secondary to sinusitis is often caused by alpha streptococci, beta streptococci, haemophilus species, and anaerobes, or mixtures of those organisms; brain abscesses secondary to chronic ear infections often include a gram-negative component with pathogens such as *E coli* or pseudomonas in combination with others; in those cases, it is important to obtain any purulent drainage from the ear canal to send for culture; brain abscess pus should also be sent at the time of surgical drainage, which is usually required for this condition; consultation with neurosurgery and infectious diseases is needed in these complicated but uncommon brain infections; brain abscesses can occur in the absence of other intracranial infections (eg, patients who use IV drugs can develop brain abscess, as can patients with endocarditis); patients with endocarditis who also have cyanotic heart disease, whether it was surgically corrected or not, are also at particularly high risk of brain abscess; patients with brain abscess of hematogenous origin often have infection due to microaerophilic streptococci, anaerobes, or mixtures of the two

Other CNS infections (e.g. subdural empyema): discussion omitted for brevity

CNS infections due to contact with the healthcare system: seem to be increasing; examples include patients with meningitis due to infection of ventriculoperitoneal (VP) shunts, intrathecal infusion pumps for drugs such as baclofen or opiates, and patients who present with infections after penetrating brain trauma, back and spine surgery, or neurosurgery; pathogens in a setting like this, in which the skull and meninges have been breached by trauma or iatrogenic interventions, is quite different from the organisms that cause community-acquired meningitis; common bacterial pathogens in these settings include coagulase-negative staphylococcus, *S aureus*, gram-negative pathogens, *Propionibacterium acnes*, candida yeasts, and other, less common organisms; probably the only pathogen that causes both community-acquired meningitis and infection following hospital interventions is *Streptococcus pneumoniae*, which can cause infections following neurosurgery, especially if there is a CSF leak; the 2017 Infectious Diseases Society of America clinical practice guidelines (published in *Clinical Infectious Diseases* spring 2018 issue) should be consulted for complicated cases following neurosurgery, external ventricular drains, ventriculostomies, VP shunts, etc.

Diagnosis: generally requires examination of the CSF; if the patient has a VP shunt or an external ventriculostomy drain, CSF can be obtained through the device rather than performing a lumbar puncture; fluid should be sent for cell counts, differential cell count, glucose, and protein, as well as for culture; CSF protein and glucose levels are important in interpreting the results of any microbiology data, especially if the organism that grows seems like a possible contaminant; a low CSF glucose level (hypoglycorrhachia) usually indicates an infection; if the CSF grows an organism that might be a contaminant, such as diphtheroids or coagulase-negative staph, if the CSF glucose, cell counts, and protein are normal and the patient has no fever, antibiotic treatment might be withheld with careful monitoring only; consultation with neurosurgery and infectious diseases is usually mandatory; removal of hardware may be required to achieve cure; empiric initial therapy for these post-neurosurgical infections generally requires IV vancomycin plus an agent with broad-spectrum activity against gram-negative pathogens, such as cefepime or meropenem

CNS viral infections: on the rise in the US; include viruses transmitted by arthropods (eg, ticks and mosquitoes); viral meningitis due to enterovirus is the most common cause of viral meningitis in the US; this infection predominates in the late summer and early fall, and is not transmitted by mosquitoes, ticks, or any other insect or arthropod vector; care for usual viral meningitis is supportive with an intent of ruling out bacterial meningitis; children and younger adults appear more susceptible to viral meningitis due to enteroviruses than do older adults

Diagnosis of enteroviral meningitis: done by viral culture of the CSF or,increasingly, by polymerase chain reaction (PCR) examination of the CSF for the virus

Arthropod-vector viral meningitides: examples of viral meningitides that are transmitted by arthropod vectors include the West Nile virus (transmitted by mosquitoes, especially mosquitoes in the genus *Culex*), Zika virus (transmitted by the tropical mosquito *Aedes aegypti)*; meningoencephalitis can also occur due to Lyme disease (transmitted by the black-legged tick, *Ixodes scapularis*, in the Northeastern US); other less common viral meningitides and viral encephalitides include the Powassan virus (transmitted by both mosquitoes and ticks), and Eastern equine encephalitis (EEE) and Saint Louis encephalitis (SLE; both transmitted by mosquitoes); confirming the viral etiology requires sophisticated testing, which is often not available in the local hospital laboratory; CSF specimens often must be sent to a state public health laboratory or the CDC; CSF testing is often based on PCR; in some cases, tests of CSF for antibody response to a pathogen can be helpful (eg, tests for IgM and IgG in response to West Nile virus infection); state public health authorities often issue warnings if there are flare-ups of these viral infections, and these warnings should be heeded; it is difficult to include a full discussion of all CNS viral infections because diagnosis depends so much on where the patient lives, their lifestyle, where they have traveled, and whether they are immunocompromised or not; must not forget

that common viral infections may disseminate to the CNS (eg, HIV and varicella-zoster virus, VZV); potent antiviral drugs active against HIV and VZV make these infections much more treatable than most of the others (eg, Zika virus); VZV infection of the CNS can be diagnosed by viral culture or PCR of CSF; IV acyclovir is useful for the treatment of VZV infections, whether in the CNS or elsewhere

Suggested Reading

Kiat HJ et al: Necrotizing fasciitis: how reliable are the signs? *J Emerg Trauma Shock* 2017 Oct-Dec;10(4):205-10; **Spellberg B, Lipsky BA:** Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis* 2012 Feb;54(3):393-407; **Tunkel AR et al:** 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. *Clin Infect Dis* 2017 Feb 14 [Epub ahead of print].

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Healthcare-associated Infections and the US Healthcare System

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Healthcare-associated Infections

Introduction: Healthcare-associated infections (HAIs) are infections that occur in patients admitted to hospital, or patients who interact with the healthcare system including: 1) patients recently hospitalized, 2) patients who attend infusion centers to receive treatment such as chemotherapy or intravenous antibiotics, 3) patients in long-term care facilities such as nursing homes; HAIs are common; each day 1 out of every 25 patients in US hospitals develops an HAI; most common infections pneumonia and surgical site infections; HAIs can significantly delay a patient's recovery; HAIs are associated with increased expense, a prolonged hospital stay, and significant patient morbidity and mortality; many HAIs are preventable; American Board of Internal Medicine (ABIM) High-Value Care statement: approximately 65-70% catheter-associated bloodstream infections and urinary tract infections and 55% ventilator-associated pneumonia cases and surgical site infections may be preventable; hospitals have shown improvement over last decade due to prevention efforts; hospitals required to report HAIs to the Centers for Disease Control (CDC) via the National Healthcare Safety Network (NHSN);recent data from CDC (2016) showed significant and promising decline in a number of HAIs; hospitals pay close attention to HAIs, since they are patient safety issue but also because they are publicly reported; therefore a hospital's reputation at risk; hospitals may also face financial penalties if HAI rates high; the Centers for Medicare and Medicaid Services (CMS) does not reimburse hospitals for some costs associated with HAIs; CMS has implemented the Hospital-Acquired Condition Reduction Program (HACRP); ranks hospitals based upon their performance, including rates of common HAIs; hospitals ranking in lowest quartile based on their hospital-acquired conditions score subject to 1% reduction in total Medicare reimbursements

Drug resistance and HAIs: prevention of HAIs is important in the era of antibiotic resistance; CDC published a comprehensive report (2013) outlining the top 18 antibiotic resistant threats in the US; included many common nosocomial pathogens including *Clostridioides difficile*, Carbapenem-resistant *Enterobacteriaceae*, multidrug-resistant *Acinetobacter*, vancomycin-resistant *Enterococcus* and multidrug-resistant *Pseudomonas*; CDC estimated at least two million people get an antibiotic-resistant infection each year and at least 23,000 people die in the US; drug resistance is common in hospitals

Antimicrobial Stewardship (AMS)

Overview: Resistant pathogens emerge in the face of antimicrobial selective pressure; antibiotics one of the most commonly administered drugs in hospitals; half of all hospitalized patients receive an antibiotic during their stay; up to 50% of antibiotic administrations are inappropriate; antimicrobial stewardship programs are critical for infection prevention; since 2017, the Joint Commission has required all hospitals and nursing care centers to have antimicrobial stewardship programs; antimicrobial stewardship consists of systematic measurement and coordinated interventions to promote the optimal use of antibiotic agents including their choice, dosing, route and duration of administration; many antimicrobial stewardship programs focus on the optimal use of broad-spectrum antibiotics and on newer antibiotics which should be reserved for the treatment of resistant organisms when other options are not available; many of the newer antibiotics are expensive; stewardship programs collaborate with infection prevention programs, eg, in the prevention of surgical site infections; issues of antimicrobial prophylaxis

Surgical site infection prevention: recommendations have changed on when and for how long to provide antimicrobial prophylaxis; In 2017 the CDC released guidelines: "for clean and clean contaminated procedures, additional prophylactic antimicrobial agent doses should not be administered after the surgical incision is closed... even in the presence of a drain;" thus the most important use of antibiotic prophylaxis is prior to incision and during the operation; ABIM High-Value Care Program also reiterated that post-operative doses of antibiotics are not indicated; important point for stewardship programs, because one of the most common indications for the use of antibiotics in a hospital is surgical site infection prophylaxis

Prevention of HAIs: most infection prevention efforts are focused around bundles of interventions that all work with the aim of preventing a specific healthcare associated infection; one of the key components of many of these bundles is hand hygiene; the most important action to prevent HAIs is effective hand hygiene; ABIM High-Value Care statement: "limiting the transmission of antimicrobial resistant organisms in healthcare settings is best accomplished by full compliance with hand hygiene protocols and contact precautions, cleaning and disinfecting the environment and patient-care equipment

before it is used for another patient, and the judicious use of antimicrobial agents"

Clostridioides difficile Infection (*C. diff*)

Introduction: *Clostridioides difficile* is an anaerobic, spore-forming, toxin-producing Gram-positive rod, previously known as *Clostridium difficile* but renamed in 2016, commonly called *C. diff*; most common cause of infectious diarrhea and substantial burden in healthcare settings, including long-term care facilities; *C. diff* infections require both colonization of the gastrointestinal tract with the organism and then exposure to antimicrobials that cause alterations in the normal flora allowing for the overgrowth of *C. diff*; hallmark of this disease is called dysbiosis (microbial imbalance) in the gastrointestinal tract; risk factors for *C. diff* colonization and infection include advanced age, multiple comorbidities, and exposure to antibiotics; exposure to the healthcare system is also a risk factor; however, the incidence of community-acquired infection is also increasing; in one recent study of community acquired *C. diff* infection, most common antibiotic exposure resulted from antibiotics prescribed by dentists; outside of the colon *C. diff* survives in spore form; these spores are resistant to heat, acid, and antibiotics but once the spores are in the intestine, they convert to their fully functional vegetative toxin-producing forms and become susceptible to antimicrobial agents; rarely invasive, and there are nontoxigenic strains of *C. diff* that do not cause infection; causes disease by releasing two exotoxins called toxin A and toxin B that cause colitis and diarrhea; one strain of *C. diff* called the NAP1/B1/027 strain (so named for the different methods of strain typing used to identify this strain of *C. diff*) linked to outbreaks since the early 2000s; considered hypervirulent for a number of reasons including its ability to produce additional toxin called the binary toxin and also its ability to produce larger quantities of toxins A and B than other strains; the amount of toxin produced by a *C. diff* strain or organism causing infection correlates with disease severity; recent data suggests the prevalence of this strain is decreasing, likely driven by significant reductions in fluoroquinolone use (to which this strain was particularly persistent) plus concerted prevention efforts

***C. diff* signs and symptoms:** watery diarrhea frequently associated with fever, abdominal pain, or cramps; severe or fulminant disease is infection characterized by ileus or toxic megacolon, defined as a maximum colonic diameter of ≥ 7 cm on X-ray; patients that develop fulminant disease may ultimately require surgical intervention; rates of colectomy range from 0.5% to 1.5% of all cases of *C. diff*

Risk factors: solid organ transplantation, haemopoietic stem cell transplants, or patients receiving cancer chemotherapy; advanced age (may be a marker for accumulation of other comorbidities), prolonged hospital stay; some of the risk factors and signs of complicated disease include profound peripheral leukocytosis which is a poor prognostic sign, renal failure, and infection with a NAP1 strain; after a first diagnosis of C. diff infection up to 30% of patients will develop at least one recurrent *C. diff* episode; risk of recurrence increases with each successive recurrence

Diagnosis of *C. Diff:* diagnosis of *C. diff* colitis challenging and controversial; asymptomatic colonization of the gastrointestinal tract with toxigenic strains of *C. diff* is common; prevalence of asymptomatic colonization with *C. diff* in hospitalized patients and patients in long-term care facilities varies; 3-25% of adult inpatients hospitals and up to 10% of elderly patients in long-term care facilities are colonized with *C. diff* without evidence of infection

Laboratory tests for *C. Diff:* variety but not one gold standard; methods detect either the organism or one or both of its major toxins (toxin A or toxin B) directly from stool samples; no test can distinguish between clinical disease and colonization; limit testing to patients with high probability *C. diff* infection; toxigenic culture and cell culture cytotoxicity neutralization assay two tests available but not used in many hospital or commercial laboratories

Enzyme immunoassays: use monoclonal or polyclonal antibodies to detect *C. diff* toxins, many commercial assays available with variable performance, less sensitive compared to some of the other tests but slightly more specific

Glutamate dehydrogenase immunoassay detects a conserved metabolic enzyme called the common antigen present in isolates of C. diff; however, this enzyme is present in all strains of C. diff, not just toxin-producing strains that cause disease; this test lacks specificity and must be combined with other testing in order to be relevant

Nucleic acid amplification testing or PCR: probably the most commonly employed test in the US, hampered by its sensitivity; detects even small quantities of toxin-producing organisms but lacks specificity; commonly picks up asymptomatic colonization and therefore should be paired with clinical parameters to improve testing accuracy

Some evidence to suggest that the level of toxin detected in stool correlates with the severity of disease presentation; 2017 Infectious Disease Society of America (ISDA) guidelines: appropriate target population for testing for *C. diff* are patients admitted to hospital (but also some outpatients) with unexplained and new-onset loose stools with at least three episodes in 24 hours and diarrheal symptoms not clearly attributable to underlying conditions (including inflammatory bowel disease, therapy such as enteral tube feeding, intensive cancer chemotherapy, or laxative use); if patients do not meet these criteria, reasonable to stop agents like laxatives; if the diarrhea persists despite withholding laxatives, then *C. diff* testing may be reconsidered; IDSA guidelines stress the importance of testing appropriate patient population and recommend two different testing strategies; if a protocol or guidelines for testing (following criteria discussed above for patients) has been implemented in an institution, then appropriate testing strategies include either nucleic acid amplification testing alone (despite the fact that it is highly sensitive) or a multi-step algorithm that combines two or three tests to improve the positive predictive value of the result; common combinations include glutamate dehydrogenase assays plus toxin assays or nucleic acid amplification testing plus toxin assays; if institutions have not implemented guidelines for *C. diff* testing, then nucleic acid amplification alone is not recommended, since a positive PCR test may reflect asymptomatic colonization; if laboratories have no clinical data and accept all unformed stools for testing,

it is most appropriate to use a diagnostic approach that includes a test that is more specific for *C. diff* infection such as a relatively sensitive toxin test as part of a multistep algorithm; testing for *C. diff* is inappropriate on formed stools (reflects asymptomatic colonization if a test is positive); frequent repeat testing within 7 days of a negative test or sending serial stool samples for *C. diff* testing after initial positive test to document clearance are also inappropriate

***C diff* prevention — antibiotic use:** most important modifiable risk factor for C. diff infection is exposure to antibiotics; almost all antibiotic agents are associated with C. diff, but most common include third and fourth generation cephalosporins, carbapenems, clindamycin, and fluoroquinolones; even very limited exposure to antibiotics (including single-dose surgical antibiotic prophylaxis regimen with a first generation narrow spectrum cephalosporin) increases the patient's risk of C. diff colonization and subsequent symptomatic disease; specific antibiotic risk determined locally; local prevalence of strains that are highly resistant to particular antibiotics may dominate

Infection control policies: *C. diff* spores are resistant to many disinfectants, contamination of the environment common; transmission in healthcare settings occurs most likely via hands of healthcare personnel transiently contaminated with *C. diff* spores or direct exposure to the contaminated environment; high-risk fomites such as electronic rectal thermometers or inadequately cleaned commodes or bed pans used for more than one patient contribute to transmission; the 2017 IDSA guidelines recommend: 1) placing patients with *C. diff* infection in a private room with a dedicated toilet; 2) ensuring that healthcare personnel use gowns and gloves upon entry and while caring for the patient with *C. diff*; 3) ensuring that healthcare personnel perform hand hygiene after removal of gloves and after direct contact with fecal contamination with hand washing with soap and water (the physical act of washing hands with soap and water is thought to improve the removal of spores from hands); using disposable equipment when possible; pay special attention to cleaning; recommendations differ depending on whether a patient has their first or a recurrent episode of *C. diff*

***C. diff* treatment:**

First episode of *C. diff:* oral vancomycin or fidaxomicin for 10 days; metronidazole is recommended as a second-line agent; for patients with fulminant *C. diff* (characterized by hypotension or shock, ileus, or megacolon), oral vancomycin is the regimen of choice; if a patient has developed ileus, the guidelines also recommend vancomycin administered per rectum and addition of intravenous metronidazole

First recurrence of *C. diff* infection: not recommended to repeat the original course of therapy used for the initial *C diff* infection; if initially treated with a course of oral vancomycin, use an oral vancomycin taper or pulse regimen or switch to fidaxomicin; however, if a patient received a course of metronidazole for initial *C diff* infection, first recurrence should be treated with a 10-day course of oral vancomycin

Multiple recurrence *C. diff:* consider fecal microbiota transfer (FMT) for patients with multiple recurrences despite appropriate medical treatment; however, this is an active area of research, some data to suggest fecal microbiota transfer for first or second recurrence of *C. diff* may be important; insufficient data to recommend as either primary or secondary prophylaxis against *C. diff* infection

Parasites: ABIM High-value Care statement: testing for parasites not recommended for patients with diarrhea lasting less than seven days or who develop diarrhea more than three days into a hospital stay; unlikely to be helpful and is expensive

Retesting for *C. diff:* ABIM High Value Care statement: patients with hospital-acquired diarrhea who test negative for *C. diff* infection should be treated with anti-motility agents; additional testing or treatment for *C. diff* not recommended

Catheter-associated Urinary Tract Infections (CAUTIs)

Overview: Urinary tract infections are the most common HAI reported to the NHSN at CDC; 75% of UTIs in hospitalized patients are associated with a urinary catheter; prolonged use of urinary catheter most important risk factor; use urinary catheters only if essential and for shortest possible duration; recommendations reinforced in High-value Care statement; asymptomatic bacteriuria common in patients with indwelling catheters and occurs at a rate of approximately 3-10% per day of catheterization; of these patients only 10-25% actually develop symptoms of a urinary tract infection; in 2009 ISDA guidelines, CAUTIs are defined as patients with: 1) symptomatic bacteriuria, ie, $>10^3$ colony forming units (CFU) per mL of uropathogenic bacteria in urine culture, 2) in a patient with UTI signs and symptoms without another identifiable source 3) in a patient with an indwelling urethral, indwelling suprapubic or intermittent catheterization; asymptomatic bacteriuria is defined as a urine culture with $\geq 10^5$ CFU/mL but no evidence of a urinary tract infection; patients who are no longer catheterized but had a urethral suprapubic or condom catheter within the past 48 hours also considered to have a CAUTI or asymptomatic bacteriuria depending on whether they meet these definitions

NHSN: uses slightly different definitions, but these definitions are used for surveillance and do not allow for attribution of fever to other infections; therefore when patients develop a fever, and urine, blood cultures and sputum cultures are all sent, a positive urine culture at that point may represent asymptomatic bacteriuria if the fever was due to another infection (for example an *E. coli* bacteremia that had developed); the NHSN definition allows for overestimating CAUTIs

Prevention of CAUTIs: relies on the appropriate utilization of catheters and the appropriate utilization of diagnostics, namely urine cultures

Appropriate utilization of catheters: appropriate indication for placing a urinary catheter includes bladder outlet obstruction or need for hourly urine output monitoring in a critical care unit; for accurate fluid intake and output measurements at the end of a day a non-invasive method such as a condom catheter or external female catheter may be indicated; ensure proper sterile technique when urinary catheter is placed and after placement, maintain a sterile continuously closed drainage system that allows unobstructed urine flow; daily reassessment to ensure that an indwelling urinary catheter is still indicated to

encourage shortest possible duration; this has reduced CAUTI infection rates

Urine cultures: only send urine for culture when a urinary tract infection is probable; typical symptoms include fever, suprapubic pain, costovertebral angle tenderness and in some cases otherwise unexplained systemic symptoms like hypotension, CIRS (chronic inflammatory response syndrome) reaction or altered mental status; patients with spinal cord injury may present with CAUTIs in atypical ways; symptoms may include increased spasticity, malaise or lethargy, or autonomic dysreflexia; urinalysis results challenging to interpret; 1) pyuria is common in patients with indwelling urinary catheters whether they are symptomatic or not; 2) the presence of bacteria on a urinalysis common whether patients are symptomatic or not; in general a urinalysis is not helpful for confirming UTI but helpful to exclude a UTI; although pyuria is not an indication that a UTI is present, unlikely to have a UTI in the absence of pyuria; urine samples for urine culture should only be obtained in patients with a high probability of a UTI, relying on the documentation of symptoms; it is not appropriate to send urine cultures in response to foul smelling or cloudy urine unless patients have symptoms suggestive of a UTI; urine samples for culture should not be obtained from an indwelling catheter or from a urine collection bag due to colonization of the actual device with bacteria (common); urine samples for culture should be ideally obtained after removal of the catheter via either a midstream urine sample or via straight catheterization; if ongoing catheterization is needed, a urine sample should be collected after replacing the catheter to avoid detecting bacteria that are colonizing the previous device

Treatment: pathogens that cause CAUTI are similar to those that cause cystitis, such as *Enterobacteriaceae*, including *E. coli*, and more commonly in the hospital *Pseudomonas aeruginosa*; note that candiduria is common in those with urinary catheters but is usually asymptomatic, representing colonization; progression to candidemia uncommon; *candida* found in urine should not be treated with antifungals; empiric therapy should be directed at pathogens listed above, considering local susceptibility data and a patient's previous urine cultures; start empiric therapy after obtaining a urine culture; therapy for CAUTIs should then be adjusted to narrowest spectrum possible as indicated by susceptibility results; duration of therapy according to guidelines is seven days in those with prompt resolution of symptoms and 10-14 days in those who do not respond as quickly; this recommendation may change over time, as it is recognized some infections may be treated for longer than necessary; in patients with a documented CAUTI, discontinue urinary catheters and transition to intermittent catheterization if needed

ABIM High-Value Care Program: states treatment of asymptomatic bacteriuria in catheterized patients is not indicated, unnecessary, and treatment may lead to harm; important to try to prevent catheter use and limit duration of use

Ventilator-associated Pneumonia (VAP)

Overview: VAP defined (IDSA 2016) as pneumonia that develops greater than or equal to 48 hours after endotracheal intubation; caused by micro-aspiration of organisms that have colonized the oropharyngeal tract or to a lesser extent the gastrointestinal tract or direct contact with environmental reservoirs, including respiratory devices or items that have been contaminated with water; VAP may be caused by a number of common nosocomial pathogens and infections can be polymicrobial; common pathogens include aerobic Gram-negative bacilli including *E. coli, Klebsiella pneumoniae, Enterobacter* species*, Pseudomonas aeruginosa* and *Acinetobacter* species; as well as gram-positive cocci, including *Staphylococcus aureus*, with specific attention paid to methicillin-resistant *Staphylococcus aureus* (MRSA), (common in many hospitals), and *Streptococcus* species; hospitalized patients become colonized with drug resistant nosocomial pathogens within days of admission; thus drug-resistant infections are a major issue that complicates the management of VAP; in one study, as many as 70% of severely ill patients became colonized with nosocomial pathogens within 48 hours of admission; the 2016 IDSA guidelines, which were jointly released with the American Thoracic Society (ATS), recommend that a clinical diagnosis be based upon a new lung infiltrate on imaging plus clinical evidence that that infiltrate is infectious; this clinical evidence may include a new onset of fever, purulent sputum, peripheral leukocytosis or a decline in oxygenation and need for more ventilatory support; no individual sign or symptom nor any combination of signs or symptoms have been found to be highly sensitive or specific for diagnosis; in many cases, it is a patient with a suspicion for VAP that doesn't have another explanation for the symptoms; differential diagnosis includes aspiration pneumonitis, which is chemical aspiration into the lungs without the presence of infection, pulmonary embolus, acute respiratory distress syndrome (ARDS), pulmonary hemorrhage, lung contusion, drug reaction, and organizing pneumonia; cultures from the respiratory tract are important in managing patients with presumed or definitive VAP; however, growth from cultures obtained through an endotracheal tube may represent colonization of microorganisms instead of organisms actually causing symptoms; important to send cultures on the appropriate patient population to appropriately diagnose disease; IDSA guidelines recommend obtaining cultures from lower respiratory tract and peripheral blood cultures when a patient is suspected of having VAP; IDSA supports the use of noninvasive culturing including endotracheal tube aspirates; (European guidelines recommend more invasive techniques, such as broncho-alveolar lavage)

Treatment: keep in mind local drug resistance patterns and patient's own microbiologic data, especially in those who are chronically ventilated; patients with suspected VAP who have risk factors for multi-drug resistant (MDR) ventilator pneumonia should receive two antibacterial agents with activity against *Pseudomonas aeruginosa* and other Gram-negative bacilli and one agent with activity against MRSA; risk factors for MDR pathogens include 1) IV antibiotics within the previous 90 days, 2) septic shock at the time of VAP (high risk if empiric regimen chosen is too narrow), 3) patients who develop ARDS preceding VAP, 4) patients who have been hospitalized for greater than 5 days prior to VAP, 5) patients receiving acute renal replacement therapy prior to the onset of VAP; consideration of local susceptibility data of multi-drug resistant *Pseudomonas* and MRSA required; in ICUs where greater than 10% of gram-negative isolates are resistant to

antibiotic being considered for monotherapy, guidelines recommend the addition of a second agent; in units in which the prevalence of MRSA is greater than 10-20% of *S. aureus* isolates in general, the guidelines recommend the initiation of empiric anti-MRSA coverage; cultures should be obtained before commencing appropriate broad empiric regimen; once the cultures return, patient should be re-evaluated to determine if changes are warranted; in patients with positive cultures demonstrating pathogenic organisms and who have improved on empiric therapy, probably do have VAP at that point, antimicrobial therapy should be pathogen-targeted; specifically, the guidelines recommend that patients that have developed VAP secondary to *P. aeruginosa* only require one effective antibiotic agent for definitive therapy and not "double coverage;" patients with negative cultures who have improved are unlikely to have VAP, assuming that the cultures were appropriately obtained prior to the initiation of antibiotic therapy; therefore clinicians should consider discontinuing antibiotic therapy; guidelines recommend seven days of therapy for patients with VAP, based on several studies that suggest that longer durations of therapy are not indicated; there is also a theory that shorter durations of therapy may reduce the emergence of resistant organisms; procalcitonin has been shown to be useful in determining the duration of therapy for patients with confirmed VAP in several studies; many institutions have instituted algorithms using procalcitonin to guide such determinations

Prevention of VAP: avoid intubation if intubation unnecessary; use non-invasive positive pressure ventilation as an alternative when feasible; limit intubation to shortest possible duration by daily readiness assessments and spontaneous breathing trials; reduce the risk of micro-aspiration by minimizing sedation and elevating the patient's bed to 30-45 degrees

Central Line–associated Bloodstream Infections (CLABSIs)

Definition: primary bloodstream infection that is not attributable to another site, meaning secondary pneumonia, in a patient with a central line that has been present for greater than two days; rates of CLABSIs have decreased over time due to prevention efforts such as bundled efforts to optimize the insertion and maintenance of the line; most CLABSIs occur outside of the ICU and in outpatients, including patients receiving chemotherapy; all types of intravascular catheter associated with risk of both local infection (redness, erythema, purulence at the insertion site) and catheter-related bloodstream infections; surgically implanted tunneled catheters such as Hickman catheters are associated with a significantly lower rate of bloodstream infection than percutaneously inserted catheters and are thus favored for intravenous access needed for a prolonged time

Risk factors: outlined in 2014 Hospital Epidemiologists of America guidelines; include prolonged hospitalization before catheterization, prolonged duration of catheterization, heavy microbial colonization at the insertion site, heavy microbial colonization at the catheter hub, internal jugular catheterization, femoral catheterization in adults, neutropenia, reduced nurse-to-patient ratio in the ICU, and the receipt of total parenteral nutrition

Prevention: bundled approaches to insertion and line maintenance; preventing infections caused during line insertion include emphasizing hand hygiene and aseptic technique and using full barrier precautions during the procedure; site selection is also important,-as most guidelines recommend avoiding femoral line placement; preventing infections during site care also includes hand hygiene and aseptic technique as well as appropriate disinfection before and after accessing the line and during routine dressing changes; the use of antimicrobial-impregnated catheters when possible and daily chlorhexidine bathing in the ICUs also recommended; reassess line necessity daily (ABIM High-value care recommendation)

Clinicians should suspect CLABSIs when a patient has evidence of infection without another source; fever is the most sensitive indicator for CLABSIs, but it is not specific, as fever in hospitals is very common; there may be local evidence of infection at the insertion site

Samples for culture: paired blood samples should be taken from the catheter as well as a peripheral vein to assist with diagnosis of CLABSI prior to the initiation of antibiotic therapy; colonization of catheter hubs is common; if the blood culture drawn through the line matches the blood culture drawn peripherally, more microbiological evidence to support the diagnosis of CLABSI

Treatment: commence appropriate empiric therapy after drawing blood cultures, providing coverage for nosocomial drug-resistant pathogens if prevalence of those pathogens is high in facility or unit; then de-escalate broad-spectrum empiric therapy to definitive therapy when blood culture and susceptibility results are available; duration of therapy depends on the organism identified from blood culture; a 14-day course of therapy may be indicated; catheter removal is important, especially for CLABSIs due to *S. aureus*, *P. aeruginosa*, fungi, or other unusual pathogens like mycobacteria; catheter salvage may be attempted when uncomplicated catheter-related bloodstream infection has been diagnosed and the organisms identified in culture are not those just listed, may include organisms such as coagulase-negative *S. aureus*; antimicrobial stewardship programs are great resources when considering salvage therapy including adjunctive antibiotic lock therapy

Suggested Reading

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Hemostasis and Thrombosis

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Introduction: hemostasis and thrombosis impact all facets of medicine (eg, stroke, cardiovascular disease, trauma, resuscitation, oral contraceptive use); complex interplay of clotting factors balancing both pro- and anticoagulant activity with interactive pathways potentiating or countering activities, respectively; Virchow's triad — any change to vessel wall (ie, endothelial injury), blood flow (either through stasis or turbulence), or constituents of circulating blood leading to hypercoagulability will predispose to thrombosis; both congenital and acquired disorders described for each component, and may be characterized as quantitative (ie, numerical deficiency) or qualitative deficiency (ie, impairment in function)

Overview of bleeding disorders: involves platelets, vascular integrity, coagulation factors; with platelets, quantitative deficiencies include production issues often due, eg, to myelosuppressive chemotherapy or irradiation; through consumption (eg, disseminated intravascular coagulation [DIC]), sequestration issue (eg, splenomegaly); qualitative platelet deficiency due to a variety of mechanisms including uremia, iatrogenic through antiplatelet agents (eg, aspirin), or bypass; with coagulation factors, quantitative deficiencies include production issues (eg, liver failure), congenital deficiencies (eg, hemophilia), consumption through DIC or inhibitors; qualitative disorders such as von Willebrand disease (VWD); vascular issues include congenital disorders (eg, Marfan syndrome or vascular malformations) and acquired disorders (eg, trauma or mechanical injury)

Overview of clotting disorders: any damage to endothelium or vessel wall can predispose to clotting; congenital disorders include AV malformations and berry aneurysms; acquired disorders (eg, trauma, neoplastic disorders, pancreatic, and brain cancers); iatrogenic disorders are common contributors to clotting risks (eg, heart valves, ports, catheters, bypass surgery, extracorporeal membrane oxygenation [ECMO]); infectious reasons (eg, syphilis, fungal disorders); inflammatory conditions (coronary artery disease); blood flow problems; stasis, if there is dehydration, can lead to thrombosis, such as sagittal sinus thrombosis; aneurysms, postoperative immobilization; turbulence from heart valves and hypertension; blood constituents' contribution to coagulability — increase in red cells or platelets; acquired disorders, eg, oral contraceptives, pregnancy, iatrogenic therapies such as prothrombin complex concentrates (PCCs) increase thrombotic risk; multiple factors compound risk

Management: management of bleeding hinges on risk-benefit analysis; is risk greater from bleeding or clotting? eg, bleeding can be treated with use of procoagulants such as recombinant factor (F)VIIa, but this carries risk of thrombosis; however, prolonged bleeding can be immediately life threatening or cause long-term adverse effects, such as hypertension, leading to neurologic or renal injury; cases need to be assessed individually; variables to be considered include acuteness of the event; management of prolonged international normalized ratio (INR) is very different 3 days prior to surgery vs assessing a patient with massive hemorrhage that needs to be reversed acutely; site of bleeding also important, eg, brain, spinal cord, eye, or lung merit much more aggressive intervention, which outweighs thrombotic risk or history of pulmonary embolus

Bleeding

Hemostasis: response to vascular injury involves activation of hemostatic pathway; normal hemostasis typically involves 3 steps: one, vasoconstriction to limit blood flow; two, platelet adhesion and activation, where there is adhesion to exposed collagen via von Willebrand Factor (VWF) and GP1B9 receptor; adhesion stimulates aggregation by 2B3A receptor and fibrinogen, generating a primary plug, which serves as substrate for the coagulation cascade; three, coagulation cascade itself, which is activated with primary endpoint being fibrin generation

Presentation of bleeding disorders: congenital factor deficiencies may present in early life depending on severity; hallmark of factor-related bleeding is joint bleeds; typical symptoms include joint pain or swelling, large hematomas following relatively mild trauma; platelet bleeding is characterized by mucus membrane low grade oozing and bleeding; may also be petechiae, ie, punctate skin bleeds; certain disorders can present with a mixed picture, ie, certain subtypes of VWD; also disseminated intravascular coagulation (DIC) eventually has both platelet bleeding and factor-related bleeding; hemostasis encompasses variety of potential disorders; any coagulation factor or aspects of hemostatic pathway may be associated with loss or deficiency, and each component is amenable to screening either looking at coagulation proteins themselves, platelet levels, or functional assays; end point of nearly all clotting tests is time to clot formation; results draw on population-based statistics to provide a percentage of normal; some non-clot based tests are immunogenic and measure factor levels directly and can detect deletions leading to low/absent factor levels, but may miss mutated, nonfunctioning factors

Prothrombin time (PT): reflects integrity of extrinsic pathway by measuring FVII activity, and also elements of common pathway (eg, FX, FV, FII, and FI) to some

extent; designed primarily to monitor the efficacy of warfarin therapy and not necessarily to screen patients for bleeding disorders; clotting is initiated by thromboplastin (commercial substitute for tissue factor) plus excess calcium (to neutralize the citrate in the blood collecting tube); sample is run at body temperature (37°C); clotting factors are temperature- and pH-dependent with narrow limits for optimal function; time to clot formation is measured and reported in seconds; prolongation of PT is consistent with deficiency in FVII; PT is sensitive to deficiencies of <30%, which is mild hemophilia range; normal clotting requires ~30% factor activity; PT is less sensitive for screening other factors in the common pathway; note that short PT is only questionably useful in predicting clotting risk

International normalized ratio (INR): a system developed to normalize PTs according to the reagents used at each facility; INR factors in individual patient's results over a PT of normal (established mean normal for your facility based on ~20-40 normal patient results); also factors in the international sensitivity index, which is calculated by the manufacturer for each lot of reagent used at your facility; INR is a way of normalizing variation across different institutions

Activated partial thromboplastin time (APTT): reflects integrity of intrinsic pathway (ie, factors XII, XI, IX, and VIII); also dependent on common pathway (factors X, V, II, and I); designed primarily to gauge the efficacy of unfractionated heparin therapy and not necessarily as a screen for bleeding disorders; clotting initiated by platelet-derived phospholipid substitute; also incorporates surface activating agent and calcium; surface agent (eg, silica) activates FXII (contact factor), starting the coagulation cascade, while phospholipid drives other factors to activate; time to clot formation reported in seconds; APTT prolongation encountered in deficiencies in intrinsic pathway factors or common pathway; can reflect deficiencies of ~<30%, mild hemophilia range; suboptimal to diagnose very mild factor deficiency levels (below normal, but >30%); APTT prolongation also seen in VWD (due to decreased FVIII levels), in DIC, where prolongation typically seen earlier than in PT (which is also affected), and also with use of heparin; recent evidence suggests that shortened APTT may be a predictor of DVT

Mixing study: if clinical history or initial screening (eg, prolonged PT or APTT) suggest factor deficiency, additional tests can identify the cause; PT and APTT prolongation can help determine where the deficiency lies; mixing study is a good first test to assess abnormalities of those 2 coagulation tests; involves generating a 1:1 mix of patient plasma and normal, healthy control plasma; this should result in at least 50% activity even in a totally deficient patient, because of the clotting factors in control; PT/APTT assays are performed immediately after mixing, and correction or lack of correction is then ascertained; PT and APTT should correct completely with mixing studies in factor-deficient patients; specimen is also incubated for 60 minutes; diminished activity following incubation is suggestive of an inhibitor; inhibitor might be specific, (eg, against FVIII) or nonspecific (eg, heparin or lupus anticoagulant)

Coagulation factor assays: perform individual factor assays if mixing study suggests factor deficiency; PT and APTT should guide testing; unnecessary to assay for every clotting factor; eg, if there's PT prolongation alone, FVII deficiency seems a rational next step; with APTT prolongation, start with FVIII, move to FIX, FXI, and ultimately FXII; both PT and APTT prolongation suggest multiple coagulation factor deficiencies, which is rare, or common pathway factor (factors X, V, II, and I) deficiencies; normal factor activity is typically 50%-150%; mild factor deficiency is typically >5% but <30% activity; moderate is >1 but <5%, and severe is typically <1% activity

Factor Deficiencies

Hemophilia A: congenital deficiency of FVIII; X-linked, so very rare in women; most common of the pure factor deficiencies, incidence of ~1 in 10,000

Hemophilia B: congenital deficiency of FIX; X-linked, so very rare in women; second most common of the pure factor deficiencies; also known as Christmas disease, named after the first patient with hemophilia B; symptoms revolve around repeated joint injuries, as chronic bleeds can lead to debilitating arthritis if not appropriately treated; patients present with prolonged APTT with correction on mixing and decreased FVIII or FIX levels in hemophilia A or B, respectively; variety of human-derived or recombinant factor replacement therapies available; dosing based on severity of deficiency coupled with need (eg, elective vs emergent surgery)

Hemophilia C: congenital deficiency of FXI; autosomal recessive and most common in patients of Ashkenazi Jewish extraction; male to female incidence is ~1:1; symptoms much less severe than in hemophilia A and B, and may not manifest until substantial trauma or surgery; not typically associated with joint bleeds, and few patients experience chronic debilitating problems; patients present with prolonged APTT that will correct with mixing, and decreased FXI level

Parahemophilia: congenital deficiency of FV; rare, autosomal recessive; called parahemophilia because it may present similar to hemophilia A, but typically only following trauma; FV and FVIII are very similar at molecular level; patients will present with both PT and APTT prolongation, and decreased FV levels

VWD: most common disorder of hemostasis; several variable deficiencies associated with VWF; VWF is important to hemostasis as it 1) offers protection for circulating FVIII and 2) is necessary for platelet adhesion through binding of platelets to subendothelial collagen by the 1B9 receptor following trauma; both quantitative and qualitative deficiencies; qualitative deficiencies refer to defective proteins which circulate at near-normal levels; 3 ways to test: 1) immunoassay to measure VWF levels, 2) ristocetin cofactor activity assay to assay VWF activity, and 3) serum protein electrophoresis (to distinguish presence/absence and size of Von Willebrand multimers); all 3 layers of testing needed to categorize deficiency

Quantitative deficiencies: type 1 and type 3; type 1 has mildly decreased VWF that functions normally; patients present with mild bleeding disorder with oozing due to the Von Willebrand-platelet interaction, or mild hemophilia-like state due to VWF-FVIII interaction;

patients may present with normal to slightly prolonged APTT and normal to mildly decreased VWF or FVIII level; type 3 has severely reduced VWF; patients present with severe bleeding disorder, which mimics hemophilia A, with some platelet-like manifestations; markedly prolonged APTT and undetectable VWF or FVIII levels; multimer analysis helps distinguish between type 1 and type 3; type 1 has all multimers but decreased in level; no multimers in type 3

Ristocetin cofactor assay: important to understand the qualitative disorders; ristocetin is an antibiotic, but no longer used because it causes thrombocytopenia and platelet aggregation; instead used to measure VWF activity; ristocetin acts via VWF and the platelet's GP1B9, primarily to induce platelet aggregation, which reflects functionality of circulating VWF; ristocetin should induce platelet aggregation in the presence of platelets and normal VWF

4 entities in type 2 VWD: type 2A is attributable to loss of high molecular weight multimers, which are the most active multimers; VW antigen levels are normal, but decreased ristocetin activity; wide spectrum of clinical presentation depending on severity of mutation and residual VWF function; patients could present with normal to prolonged APTT, normal VWF levels, but decreased ristocetin activity

Type 2B: has a defect which causes VWF to bind platelets avidly; clears both VWF and platelets from circulation, so these patients present with normal VWF level with decreased ristocetin activity and mild thrombocytopenia; mutation also leads to mildly decreased FVIII levels; clinically it presents as mild to moderate bleeding disorder, and diagnosis is best made through platelet aggregation studies; findings likely attributable to high molecular weight multimer loss

Type 2N: other 2 entities in qualitative VWD spectrum are type 2N (N for Normandy) and 2M; type 2N has a defect in VWF binding to FVIII; VWF, ristocetin activity, and multimers are normal, but FVIII levels may be severely reduced and APTT consequently prolonged; difficult to distinguish from hemophilia A; there should be some level of suspicion if a female patient presents with hemophilia A history; Likewise a nonresponder to FVIII treatment; diagnosed by DNA or familial analysis

Type 2M: has a mutation of the binding site for platelet 1B9 receptor, so normal platelet adhesion cannot occur; patients present with oozing and mucus membrane-associated bleeding; VWF and multimer analysis are normal, ristocetin activity is decreased; FVIII levels are low to normal, so APTT is normal; diagnosis requires complex antigen structure analysis and platelet aggregation studies with and without normal plasma

Acquired factor deficiencies: 2 most common mechanisms for acquired factor deficiencies are first, iatrogenic, where some level of anticoagulation is induced; eg, warfarin, heparin (which inhibits factor assay), new oral anticoagulants; second, abnormal factor consumption through bleeding, DIC, massive trauma, or transfusion; third, (comparatively rare) are immune causes of deficiency; rarely non-hemophilia patients will acquire autoantibodies to a circulating coagulation factor; typically occurs idiopathically, but can be encountered in pregnancy, paraneoplastic disease, or autoimmune disease

Transfusion management in bleeding patient: blood is a transplant and requires compatibility testing; blood groups — 2 most well-known blood group systems are ABO and Rh (rhesus); both systems are highly immunogenic; ABO has naturally occurring antibodies; Rh requires exposure, ie, transfusion or pregnancy; antibodies can result from exposure, and when re-challenged can lead to major acute hemolytic transfusion reaction or in case of pregnancy, to hereditary disease of fetus or newborn when maternal antibodies cross the placenta and cause hemolysis in fetus; we make antibodies to what we lack; in ABO system, group A has A antigen, so we produce anti-B; group B has B antigen, so we produce anti-A; group O lacks both A and B antigens, so group O individuals are universal donors, and produce anti-A and anti-B; group AB are universal recipients because they have both A and B antigens, and make no ABO antibodies; platelets express ABO; very few red cells, because we now collect with efficient technology, but platelets express HLA (human leukocyte antigen); plasma contains the antibody portion of blood, so compatibility is reversed; eg, compatible plasma for group B patient would be group B or AB plasma

Important terminology: "type" refers to ABO and Rh D typing; A pos means group A and positive for Rh D antigen; when we "screen," patient plasma is mixed with 3 screening red cells of known phenotype and represent the major significant red cell antigens; are >30 blood group antigen systems, many of which are clinically significant; if screen is positive, time to obtain compatible blood depends on the nature of that specific antibody — could be very short or very long time; also important to know if patient has known history of antibodies, as antibodies below detectable levels may be missed in screening; also depends on whether patient has been transfused recently; depends on availability of "cross match" compatible blood; for cross match, patient plasma is mixed with a sample of donor red cells to assess for compatibility; look for hemagglutination; finding cross-match compatible blood can be difficult if patient has multiple antibodies, autoantibody, or antibodies against a high-prevalence antigen

Transfusion triggers: red cells, platelets, plasma, and cryoprecipitate are all integral to management of the bleeding patient; 1 unit of red cells should increase the hemoglobin by 1 g/dL, or the hematocrit by 3%; triggers have become much more conservative; most stable patients do not need to be transfused above a hemoglobin of 7 g/dL

Platelet transfusion: 1 unit of platelets is expected to raise platelet count by ~30,000-50,000; triggers for platelet transfusions differ depending on whether platelets needed for prophylaxis or active bleeding; most platelet transfusions occur prophylactically; platelet triggers — in stable, non-bleeding patient (eg, oncology setting), target is platelet count of 10,000; patient with sepsis but not active bleeding, target is 20,000; if invasive procedure (eg, lumbar puncture) planned, or patient is bleeding, target is 50,000; if history of bleeding or risk of bleeding at sensitive site like brain or eye, target is 100,000; these numbers are arbitrary and controversy exists; post-transfusion counts should be drawn 10-60 minutes after transfusion; corrected counts increments (CCI) can be calculated to guide the response; need to draw 2 samples

at different times (within the 10-60 minute window); refractoriness to platelet transfusion can be immune or nonimmune; nonimmune causes include fever, bleeding, splenic sequestration (as in enlarged spleen or sepsis); immune causes include HLA and/or antibodies against platelet-specific antigens

Plasma transfusion: plasma rarely needs context; is very contentious, because there's often request to transfuse for patients who are not actively bleeding, but there's a perceived need to reduce the INR to low levels; plasma has no place in correcting bleeding risk for an INR <~1.7; cryoprecipitate is indicated for fibrinogen supplementation and can be used in massive transfusion or patients who are bleeding with fibrinogens of <150; massive transfusion is associated with deadly triad characterized by hypothermia (from blood being refrigerated), hypercoagulability (partly due to cold, also dilution effect and consumption), and acidosis (due to cold and tissue ischemia); huge strides and advances in resuscitation, largely from what has been learned in Iraq and Afghanistan wars; with early diversification of products, red cells, platelets, plasma, optimal transfusion ratio is approximately 1:1:1, and there is growing support for whole blood transfusion in the setting of trauma and resuscitation

Transfusion reactions: several types; febrile nonhemolytic transfusion reaction characterized by increase in temperature, rigors, and chills due to cytokines in the blood product, generally uneventful response to Tylenol; allergic reaction ranging from mild urticaria to (rarely) anaphylaxis, and are response to plasma proteins; septic or bacterial contamination reaction primarily affecting platelets; symptoms are nonspecific and overlap with other reactions; patients present with fever, hypertension, and rashes; hemolytic transfusion reactions can be acute; most common reason is clerical error; delayed hemolytic transfusion reactions are called anamnestic or waking up of an antibody which has been suppressed, a patient developed an antibody in the past, screen is negative, but on re-challenge that antibody can cause delayed hemolysis, approximately 7- 12 days post-transfusion; 2 very serious transfusion reactions are transfusion-associated circulatory overload (which is really pulmonary edema secondary to transfusion) and transfusion-related acute lung injury, an immune phenomenon not totally well understood, may be ascribed to HLA antibodies in the donor product reacting with cognate antigens in the recipient and leads to lung injury, where patients typically deteriorate, require intubation, and either recover or die; carries a significant mortality

Complementary therapies for bleeding: antifibrinolytics (eg, aminocaproic acid [Amicar]); prothrombin complex concentrates (PCCs) differ by the number or type of clotting factors they contain and whether activated; recombinant FVIIa, which is most often prescribed for off label indications of bleeding, few labeled uses such as FVIII or FIX deficiency with inhibitors or congenital deficiency in FVII; PCCs and recombinant FVIIa carry some level of thrombotic risk, can be expensive, highly variable dosing depending on the indication, consultation with someone with experience with these products recommended

Clotting

Natural anticoagulant systems: prevent formation and/or propagation of clots — antithrombin (AT), protein C, protein S, and plasminogen; generally inactivate or downregulate coagulation factor activity; disorders/deficiencies of natural anticoagulants can lead to abnormal clotting or hypocoagulability; AT irreversibly inhibits coagulation factors with primary target being FXa and FIIa (thrombin); AT deficiency can lead to unchecked thrombin activity, can be acquired or hereditary; acute clot formation, heparin therapy, and acute illness (eg, sepsis) can transiently decrease AT levels; unclear if these risks equate to thrombophilia; hereditary deficiency can be homozygous or heterozygous; heterozygous more common, carries about 3-7-fold increased risk for thrombosis; homozygous deficiency is rare, causes fatal clotting; AT pitfalls — testing is complex, using a chromogenic substrate assay, but AT levels should be interpreted with caution in acutely ill patients, patients immediately after clotting, or patients receiving heparin therapy, because all may be associated with decreased AT levels; best to repeat levels when patient is stable or off heparin; human-derived and recombinant AT concentrates are dosed once per day for congenital deficiency; former has longer half-life, latter also used for prevention of venous thromboembolism; no strong evidence-based recommendations for acquired deficiencies; use 500 unit vial of human-derived AT concentrate in the setting of heparin resistance; 2nd dose can be considered if no response to the 1st dose; alternatively, plasma is an excellent source of AT, so 2-4 units of plasma can help overcome heparin resistance

Protein C and protein S: 2 interconnected vitamin K-dependent anticoagulants; thrombin complexes with thrombomodulin, which converts protein C to activated protein C (APC); APC binds protein S to maintain activity, and inactivates coagulation factors, primarily FVa and FVIII

Protein S deficiency: can be congenital or acquired; acquired protein S deficiencies include post-clot formation during pregnancy, warfarin use, or vitamin K deficiency; unclear risk for thrombophilia; congenital deficiencies rare; heterozygous are most common, carry variable risk for clotting, 5- to 10-fold; homozygous is extremely rare and likely fatal; 3 classes of protein S deficiency; type 1 most common, followed by type 3; quantitative defects with decreased production or increased clearance; associated with stress, pregnancy, congenital decrease in protein S production, or binding to C4b; type 2 rare; qualitative or functional deficiency; testing and classification of protein S deficiencies employs both activity and antigenic assays

Protein C deficiency: can also be congenital or acquired; acquired can be post-clotting or associated with vitamin K deficiency from warfarin; unclear risk for thrombophilia; congenital deficiencies fairly common; heterozygous most common, has mildly increased clotting risk, less than with protein S deficiency; homozygous very rare, likely fatal; testing and deficiency identification rely on activity and antigenic assays; are protein C deficiency subtypes; type 1 more common, quantitative defect with decreased activity and decreased total antigen; type 2 rare, with decreased activity but normal antigen levels; pitfalls are that protein S and C

levels cannot be accurately determined in patients on warfarin; prolonged PT in conjunction with decreased levels suggests warfarin; repeat testing is recommended for acutely ill patients or those following an acute clot; treatment is the same for most congenital deficiencies; for patients with severe congenital protein C deficiency, recombinant protein C concentrate no longer available, but there is supressin, a human-derived or fractionated plasma product; but would need hematology consultation

Factor V (FV) mutations: change conformation and render FV resistant to deactivation by APC; several mutations have been described, all can cause thrombophilia; most well-known is factor V Leiden (FVL), in which arginine is replaced by glutamine, and which accounts for 85%-90% of cases; FVL inherited autosomal dominant; homozygotes carry ~50-80-fold increased thrombotic risk vs 4-8 fold in heterozygous individuals; ~3%-8% of white race are FVL carriers; ~30% of people with DVTs are found to have at least 1 abnormal copy of FVL gene; testing for suspected mutations in FV should start with examination of resistance to deactivation by APC; resistance is suggestive of FV mutation but not specifically FVL; in a PTT-based method, patient plasma is mixed with normal control, with and without APC component; in a normal individual PTT should be prolonged in presence of APC, and normal without APC; ratio of PTT with APC to PTT without APC if >2-2.5 is consistent with a normal FV; ratio <2-2.5 suggests abnormal FV; molecular testing should follow after demonstration of APC resistance; in case of familial thrombophilia with suspected FV mutation, always recommend APC resistance as the first test, because FVL testing alone may miss up to 5%-10% of FV mutations; APC and FVL testing can be performed in patients on warfarin, as assessment is of FV, not APC; heparin can be problematic for APC, because it's a PTT based assay; FV level testing inappropriate in thrombophilia, because levels will be normal in FV mutation

Prothrombin mutations: mutations in FII; second most common form of inherited thrombophilia; ~1 in 50 white individuals are heterozygous; rare in non-white; homozygosity very rare; much more mild form of thrombophilia, heterozygotes have ~3-fold increased thrombotic risk; point mutation at position 20210 in a noncoding region of FII nucleotide, causing increase in prothrombin levels, and correlates with slightly higher tendency to form clots; does not render FII resistant to deactivation; thrombin level measurements not recommended for screening due to broad reference range; in patients with hereditary thrombophilia and recent thrombosis, direct testing for prothrombin mutation is warranted, and may be considered first-line approach in evaluation

Plasminogen: liver-derived natural anticoagulant, circulates as inactivated plasminogen; is cleavaged to plasmin upon activation, causing lysis of fibrin-based clot; plasminogen-to-plasmin cleavage (and thus plasminogen activity) is indirectly controlled via inhibition of tissue plasminogen activator (tPA) and urokinase (uPA) by plasminogen activator inhibitor; deficiencies of plasminogen can be congenital or acquired; congenital are very rare; few reported cases of heterozygous or homozygous deficiencies; limited data suggests that this may not be a substantial thrombotic risk factor; causes of acquired deficiency, such as end stage liver disease and DIC, may be associated with thrombosis; testing is complex and involves mixing patient plasma with uPA; uPA cleaves plasminogen to plasmin, which combines with a chromogenic compound measurable by spectrophotometry; concentration correlates with plasmin activity; pitfalls are that plasminogen activity cannot be accurately determined in a patient on antifibrinolytic therapy (eg, Amicar); repeat testing is recommended for acutely ill patients or those immediately post-clotting or in DIC; normal test results do not exclude other deficiencies of plasmin pathway; for management, no clinically available plasminogen concentrate in US

Antiphospholipid syndrome (APS): characterized by presence of antibodies against phospholipids, and/or coagulation factors bound to phospholipids; diagnosis requires both clinical and laboratory criteria (at least one of each); antibodies include anticardiolipin antibodies, lupus anticoagulant (LA), anti-beta-2 glycoprotein 1 antibodies, and anti-protein thrombin antibodies; patients present with thrombosis, typically recurrent thrombi (arterial or venous) and small vessel thrombi; mechanisms of antibody activation are not well understood, may be secondary to factor activation, inhibition of natural anticoagulants, or disruption of endothelium; patients can present clinically with livedo reticularis (fishnet stocking rash); APS also presents with many complications in pregnancy (eg, recurrent spontaneous abortion, unexplained death of normal fetus, placental insufficiency, and/or eclampsia); APS not necessarily associated with lupus or other autoimmune disorders; laboratory findings may include antibodies, thrombocytopenia, and a prolonged PTT (not always found)

Diagnosis of LA: several criteria must be met — prolongation of 1 phospholipid-dependent clotting test such as PTT and/or dilute Russell viper venom time, lack of correction of one of those tests with plasma based-mixing study, indicating a factor inhibitor, and correction of those test abnormalities with addition of phospholipid; in dilute Russell viper venom time test, viper venom is added to control and patient plasma samples to activate FX and time to clot formation is measured in each sample; if ratio of patient to control >1.2, consistent with presence of LA; in a Staclot LA assay, addition of hexagonal phase phospholipids (which are more specific for LA) should correct clotting tests if LA is present; presence of LA does not necessarily mean patient has APS; since LA-like activity can be seen post-infection or in acute stress; testing must be repeated on 2 occasions approximately 12 weeks apart per consensus criteria; as a pitfall, anticoagulants can severely interfere with LA testing, causing elevations in Russell viper venom time; interferences from heparin, warfarin, oral anti-FXa agents, direct thrombin inhibitors; good to check anticoagulant status with isolated prolongation of Russell viper venom time

DVT and PE: D-dimer is a measure of cross-linked fibrin breakdown; highly sensitive, elevated in almost all patients with acute DVTs, low specificity; elevated in surgery, trauma, sepsis, pregnancy, renal failure, and others; clinically, DVTs present nonspecifically; swelling is most common (97%); pain (86%), warmth (72%); because symptoms are nonspecific, differential is broad,

and includes cellulitis, venous valvular insufficiency, etc.; pretest probability guides follow-up steps using D-dimer vs compression ultrasound; Wells score is well-validated in generating probability; scoring is based on clinical findings (eg, edema) and risk factors (eg, immobilization or cancer); low probability score will use D-dimer to guide if further testing is indicated; high probability score suggests proceeding to compression ultrasound

Pregnancy and thromboembolic disease: risk increases dramatically during pregnancy; thromboembolic risk is multifactorial, includes hypercoagulability, decreased protein S, increase in multiple clotting factors, endothelial and anatomic changes, and pathological associations with pregnancy; D-dimer is not useful in pregnancy, so proceed directly to ultrasound or imaging

Anticoagulants: warfarin among most commonly utilized anticoagulants in hypercoagulable patients; results in deficiency of vitamin K-dependent clotting factors (FII, FVII, FIX, and FX, as well as proteins C and S); following ingestion, all vitamin K dependent factors will begin to decrease; FVII is most sensitive to warfarin therapy because of its short in vivo half-life of ~4-6 hours, but anticoagulant effect may not be seen until several doses; need for bridging, as anticoagulant effects of protein C and S decrease early; since FVII is very sensitive to warfarin, PT is used to gauge therapy efficacy, and goal prothrombin time is ~2-3 times the upper limits of normal for most hypercoagulable patients; with heparin, mechanism of action is to potentiate antithrombin III effects; activity of antithrombin III immediately enhanced after administration; types of heparin include unfractionated, low molecular weight; antidote is protamine with rapid reversal; in heparin-induced thrombocytopenia, antibodies bind to complexes of heparin and platelet factor IV, activating platelets and promoting prothrombotic state; since heparin primarily effects FX activity, APTT is used to gauge efficacy of heparin therapy; goal PTT is typically 1.5-2 times the upper limits of normal for most hypercoagulable patients; very high doses can also prolong PT; with respect to heparin vs warfarin, mixing study used to determine cause of prolonged PT or APTT; PT prolongation due to warfarin should fully correct as we're replacing deficient factors; APTT prolongation due to heparin will not correct as we cannot overcome the antithrombin effects; mixing studies can be followed by protamine or polybrene addition to sample, which bind heparin and inactivate it; correction of prolonged APTT with such addition is consistent with heparin

Antiplatelet agents: 3 classes; first, aspirin, which blocks cyclo-oxygenase 1 (COX1) in platelets, which is needed to generate thromboxane A2, a platelet activator; second, agents which target P2Y12 and inhibit P2Y12; eg, clopidogrel, which blocks aggregation by interacting with 2 receptors P2Y1 and P2Y12; this is metabolized by the CYP2CY9, which is subject to drug interactions; polymorphisms impact availability of active form of drug; newer agents less susceptible to this problem; third, G2b3a inhibitors, eg, abciximab, which inhibit platelet aggregation mediated via fibrinogen; G2B3A inhibitors have a quick onset and quick offset for use

New oral anticoagulants (NOACs): target activated FII or FX; dabigatran, direct thrombin inhibitor, has a reversal agent, idarucizumab; 3 anti-FX inhibitors — rivaroxaban, apixaban, and betrixaban; a reversal agent has been recently approved, andexanet alfa; agents are useful because they are oral, have predictable and reliable pharmacokinetics independent of diet (so predictable dosing), there can be selective problems in the cases of renal insufficiency, such as with dabigatran; generally have little to no effect on standard coagulation assays, thus hard to monitor

Suggested Reading

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Dementia, Delirium and Assessment of Decision-making Capacity

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Dementia: prevalence increases with age (5% in 71 to 79 years; 38% in 90 years and older); prevalence increasing more in low to middle income countries; Alzheimer's disease (AD) is most frequent type; 5.3 million persons currently have dementia; expected to increase to 13.8 million by 2050; only one of top 10 causes of death in US that cannot be prevented, cured, or slowed

Case: Mr. Hamilton is a 77-year-old retired high school math teacher, married to Joan for 50 years, 3 sons and 7 grandchildren lives in California; enjoys movies, museums, plays, dinner with friends; loves grandchildren and planning trip with wife to visit them next month; prostate cancer diagnosed 18 years ago, now metastatic to bones, lymph nodes, and lungs; radical prostatectomy, external beam radiation therapy, and androgen deprivation therapy; hypertension (controlled on atenolol, hydrochlorothiazide, losartan, amlodipine for 15 years); forgetfulness for last year, worse since androgen deprivation therapy; some functional changes (difficulties with paying bills and word finding, and getting lost in unfamiliar places); wife is concerned about his forgetting blood pressure medications; at medical oncology visit, complained of muscle aches, lower extremity edema, diarrhea, and urinary urgency; blood pressure, 179/102; sodium, 122; WBC, 14,000; BUN, 40; creatinine, 1.5; what is differential diagnosis? patient declines hospitalization; how would you assess capacity to decline hospitalization? how would you manage patient?

DSM-5 criteria for dementia: 1) evidence of significant cognitive decline from previous level of performance in 1 or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual, motor, or social cognition); cognition comprised of attention, executive functioning, memory, language, and visuospatial function (decline in cognitive domain of memory not necessary); decline must be new; 2) cognitive deficits interfere with independence in everyday activities; patient requires assistance with complex independent activities of daily living (ADL), such as paying bills, managing medications, shopping, housekeeping, accounting, food preparation, transportation, ordering from menu; in mild cognitive impairment (in contrast to dementia), no change in functioning or independence; 3) cognitive deficits not exclusively in context of delirium; 4) cognitive deficits not better explained by another mental disorder (schizophrenia, major depression); dementia is global decline of cognitive capacity; clear consciousness and alertness until very advanced stages (versus delirium); multiple areas of cognition affected

Epidemiology: AD — most common (50% to 75%); vascular dementia; mixed type dementia, common but difficult to rule out without autopsy; dementia with Lewy bodies; frontotemporal dementia (frontotemporal lobar degeneration); advanced AD is one of top 10 causes of death in US; in 2040s and 2050s, expect increasing number of older adults with dementia syndromes as people living into 80s, 90s, and 100s

Mild cognitive impairment (MCI): not dementia; cognitive disturbances in MCI do not impair independence and ADL; 5% to 10% progress to AD/other dementia; annual follow-up with cognitive and functional assessment; some patients do not progress; subjective complaints, not cognition

Alzheimer's disease: deficits primarily in memory plus at least 1 other domain; confirmation at autopsy; characteristic clinical features; short-term memory difficulties common

Vascular dementia: clear temporal relationship with vascular event; vascular risks (hypertension, diabetes, smoking, hyperlipidemia, family history); cognitive deficits may be independent of motor/sensory sequelae of vascular event

Dementia with Lewy bodies: central feature not memory difficulty; attentional deficits, visuospatial deficits, executive dysfunction; core features are visual hallucinations, visuoperceptual disturbance, Parkinsonism, fluctuations in cognition by hour or day; most difficult dementia to differentiate from delirium; differs from Parkinson's disease-related dementia in time of onset of cognitive deficits; can develop Parkinsonian symptoms within 1 year after cognitive symptoms; Parkinson's patients usually take longer to develop dementia; Lewy body-related dementia characterized by REM sleep behavior disorder and neuroleptic sensitivity; if hospitalized patient with behavioral disturbances has history of neuroleptic sensitivity, never treat with neuroleptics/anti-psychotics; REM sleep behavior disorder (bed partners complain about being hit and kicked because patients act out dreams) may predate dementia by decades; assess and monitor patients with REM sleep disorder for development of dementia with Lewy bodies

Frontotemporal dementia (frontotemporal lobar degeneration): behavioral disinhibition; significant personality changes — apathy, loss of empathy, perseveration, compulsive behavior, ritualistic behavior, hyperorality, dietary changes; memory usually unaffected; may have executive dysfunction; are non-behavioral variants; primary progressive aphasia presents with

language deficits requiring assessment in memory disorder center

Differential diagnosis of mild cognitive deficit: importance of degree of interference with independence and ADL, especially with complex tasks; patient less efficient in mild cognitive impairment but no significant interference; other conditions can cause mild cognitive impairment, such as psychiatric diseases, particularly depression; depression may present with cognitive rather than mood symptoms, especially in older adults; on Mini Mental Status Examination or Montreal Cognitive Assessment Test, depressed patients tend to answer "I don't know;" in true cognitive impairment, patients show effort in answering; sleep disturbances can cause mild cognitive impairment, especially in older adults; medications (especially anticholinergics or antihistamines); metabolic disturbances (vitamin B12 deficiency, hypothyroidism); neurologic diseases (cerebral vascular disease, epilepsy, multiple sclerosis, brain tumor, Parkinson's disease)

Pathophysiology of dementia: except for vascular dementia, pathological accumulation of native protein in brain causes synapse and neuronal loss and brain atrophy; in vascular dementia, injury to brain tissue causes synapse and neuronal loss; in AD, brain biopsy or autopsy shows extracellular plaques of amyloid or intracellular tangles of hyperphosphorylated tau protein (plaque and tangle pathology); amyloid accumulation, extracellular; tau accumulation, intracellular; brain Lewy body pathology is distinctive; frontotemporal lobar degeneration has deposition of ubiquitin; currently no clinical role for biomarker assessment in AD because there is no disease-modifying therapy and testing is expensive

Biomarkers: core CSF biomarkers (amyloid beta-42, T tau, and P tau) can identify prodromal AD in MCI stage with 85% to 90% sensitivity and specificity; cortical deposition of amyloid beta-42; total tau (T Tau) levels reflect intensity of neurodegeneration; phosphorylated tau levels (P tau) correlate with neurofibrillary pathologic changes; imaging important, as regional atrophy in medial temporal region can be diagnostic for AD (especially on MRI); hippocampal atrophy (if no hippocampal atrophy, AD unlikely); FDG (fluorodeoxyglucose) PET can be very sensitive for synaptic dysfunction (negative scan, no neurodegenerative disease); positive FDG PET shows temporal, parietal, and posterior cingulate atrophy; in frontotemporal dementia, PET differentiates from AD because of anterior frontal area changes; genetic biomarkers important; apolipoprotein E4 allele associated with increased risk of AD (and "chemobrain" [cancer and cancer treatment-related cognitive changes])

Assessment of cognitive symptoms: history from patient and caregiver; ask about cognitive changes from baseline and functional deficits; medical history to assess vascular risk factors, hypothyroidism, illicit drug use, medications; investigate home circumstances (does patient live alone? what are safety measures? Does patient drive? does patient use alcohol or smoke?); alcohol important cause of dementia; family history; repetitive questioning, inability to navigate journeys (especially in less familiar environments); difficulty recognizing previously familiar people; difficulty using new equipment; word finding difficulty; participates less in group conversations; less attention to personal hygiene or appearance; short-temperedness with family; more irritability or agitation, especially in evenings; in later stages, not recognizing home; safety concerns of driving, kitchen, cigarette disposal, wandering, handling of money; on physical exam, extrapyramidal signs, focal neurologic deficits (especially for vascular dementia), ability to follow instructions; check pulse, auscultate chest to assess for cardiac issues (atrial fibrillation or stroke); Mini-Mental Status Exam or a Montreal Cognitive Assessment tool; latter gives better idea of performance level in different cognitive domains, more difficult compared with MMSE, which may have false negatives in high-functioning person; if behavioral disturbances, neuropsychiatric inventory, especially when medications started; activities of daily living scales; if concern for depression, Geriatric Depression Scale helps distinguish between depression and dementia in older adults; behavioral scale factors of delusions, hallucinations, agitation, aggression, apathy, disinhibition, sleep and appetite change; neuropsychiatric testing to assess disturbances across many cognitive domains; used commonly to assess cognitive changes related to cancer and cancer treatment (minor but disturbing to patients); drawbacks to neuropsychological testing — testing is lengthy, and you may not know patient baseline; test based mainly on age and educational level; expensive; laboratory testing — check TSH, vitamin B12 levels; American Academy of Neurology recommends structural neuroimaging (non-contrast head CT or MRI) in initial evaluation; consider EKG for vascular risk factors (atrial fibrillation); Mini-Cog, simple screening test, is a 3-word registration and recall plus clock drawing; 97% sensitivity and 95% specificity for dementia; not helpful to assess a previously high functioning person; Mini-Mental Status Exam is copyrighted (need to pay for it); Montreal Cognitive Assessment test is translated into multiple languages and has a few versions (use if need to repeat test); total score of 26 is normal for patients with 12 or less years of education

Stages of Alzheimer's disease: mild AD, forgetfulness, poor judgment, apathy, pretension, difficulty with complex tasks, depression, and trouble at work; moderate AD, disorientation, more severe memory loss, confusion, sleep difficulties, wandering, speech difficulty, restlessness, behavioral symptoms; severe AD, agnosia (inability to identify objects despite intact sensory functioning), apraxia (inability to carry out motor activities), aggression, agitation, incontinence, significant impairment of independent activities and basic activities of daily living, gait disturbances, profound memory deficits (inability to recognize family), minimal verbal communication, loss of ambulatory abilities, inability to perform activities of daily living, may have urinary and fecal incontinence; most common clinical complications are eating problems, infections; need for advanced care planning to guide treatment decisions, with patient comfort as primary goal; observational studies show no benefits of tube feeding but benefits of hospice care

Uncommon forms of dementia: progressive supranuclear palsy, multi-system atrophy, corticobasal degeneration, normal pressure hydrocephalus, Creutzfeldt-Jakob disease

Screening: per US Preventive Services Task Force, insufficient evidence to recommend for or against routine dementia screening in older adults; American Academy of Neurology and the Canadian Task Force on Preventive Healthcare do not endorse screening or recommend against

it in asymptomatic adults; there are no disease-modifying agents for dementia; neurosyphilis screening not routinely recommended unless high suspicion based on sexual history or travel to areas where exposure may be common; HIV screening appropriate in certain patients

Memory problems in cancer patients: subjective reports of memory difficulty more likely due to attention disturbance; patients do not remember information that is presented because they have never registered it due to poor attention; common to use medication to boost attention in patients with impairment in day to day functioning; oncologists need to screen patients for cognitive deficits at baseline, especially as many of them are elderly; any oncology treatment (chemo or radiation or immunotherapy) can cause cognitive impairment ("chemobrain" changes); pre-treatment studies in patients with breast cancer show subtle cognitive impairment at diagnosis, likely due to inflammation response

Treatment of dementia: cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and NMDA receptor antagonist (memantine); no treatment is disease modifying; rivastigmine patch available; no pharmacologic intervention provides significant benefit; newly diagnosed AD, start with cholinesterase inhibitor; weaker recommendation to start cholinesterase inhibitor for newly diagnosed vascular dementia, Parkinson's dementia, or Lewy body dementia; medications do not change cognitive impairment, but may slow decline and improve neuropsychiatric symptoms; unclear whether improvements are clinically significant (eg, slowing of decline in MMSE by 1 point per year); important to discuss expectations and side effects with patient and family to make informed decisions; in moderate to advanced dementia, can add memantine to cholinesterase inhibitor or use memantine alone; in severe dementia, can continue mamentine, but comfort should be priority, and decision to discontinue medication is reasonable

Behavioral disturbances: difficult because usual medications have side effects, especially in older adults with dementia; nonpharmacologic interventions — caregivers or nursing homes may use evidence-based aromatherapy, music therapy, pet therapy, physicality-based treatments (yoga or dance), other treatments to improve physical abilities; behavioral redirection, verbal redirection; minimize use of psychotropic medications; consider anti-psychotics if patient has significantly disturbing behavior or presents risk to self or others; need to regularly re-assess need and dose to minimize side effects; neuropsychiatric symptoms common (delusions, hallucinations, depression, anxiety, agitation, aggression, euphoria, irritability, disinhibition, pacing, wandering, and sleep disturbances); symptoms can cause significant caregiver distress and admission to long-term care facilities; first step is to identify precipitating factors and treat medical conditions that cause superimposed delirium; address underlying reversible causes; environmental, behavioral, and other non-pharmacological therapies should be preferred over medications; pain important cause of behavioral disturbances; cholinesterase inhibitors do not produce clinical improvement in neuropsychiatric symptoms in patients with dementia; selective serotonin reuptake inhibitors (SSRIs) can be tried for depressive symptoms; citalopram often used (shown to have benefits for neuropsychiatric symptoms); limit citalopram dose in patients over 60 years old to 20 mg/day; sertraline is well-studied alternative; avoid tricyclics (side effects); anti-psychotics have limited efficacy, associated with increased mortality in patients with dementia, but may have no alternatives if disabling, threatening behavior that puts patient and others at risk; use low doses of anti-psychotics; olanzapine and risperidone preferred; use short-term with regular reassessment; weigh risks and benefits; patients with dementia of Lewy bodies at high risk of severe side effects with neuroleptics; when pharmacotherapy necessary to treat behavioral symptoms in patients with dementia of Lewy bodies, can consider using low-dose quetiapine or clozapine; clozapine studied in patients with Parkinson's disease-related dementia and behavioral disturbances, but not really practical because of need for frequent blood tests regardless of dose; avoid physical restraints, as they can increase risk to patients; only use physical restraints for patients who pose imminent risk of physical harm to themselves or others; only use for very short periods of time; for significant apathy, could consider antidepressants, psychostimulants, or cholinesterase inhibitors; sleep disturbances challenging, but use non-pharmacological strategies; sleep medications (especially benzodiazepines) cause significant side effects for patients with dementia; medications with anticholinergic or antihistamine effects should be avoided in older adults; melatonin and ramelteon could be alternatives for sleep disturbances

Delirium: a diagnosis that patients and families suffer from; one of the most common and serious neuropsychiatric complications seen in medically ill patients; associated with increased length of hospitalization, higher health costs, significant distress to patients, family, and caregivers; associated with long-term adverse cognitive outcomes and functional dependence; frequently under-recognized, misdiagnosed, untreated or inappropriately treated; interferes with assessment and management of medically illness (most significantly and commonly with pain); may be harbinger of impending death in palliative care; need to be able to diagnose, assess etiologies, and understand the risks and benefits of interventions; delirium defined in 1st century by the physician Celsus, who said that "sick people, sometimes in a febrile paroxysm, lose their judgment and talk incoherently; when violence of the fit is abated, the judgment presently returns;" the current definition of delirium is acute onset change in mental status characterized by a disturbed level of alertness, inattention, fluctuating course, cognitive and/or perceptual disturbances, due to an underlying medical condition or medications; different terminology across disciplines complicates diagnosis; neurologists refer to "toxic-metabolic encephalopathy;" "sun-downing" commonly confused and used interchangeably with delirium; "ICU psychosis" used by ICU clinicians; "acute brain failure" might be a better term

Prevalence: in hospital, 10% to 25%; older adults, prevalence much higher; in ICU, 20% to 80%; post-surgically, 15% to 50%; palliative care settings, up to 85%; any acute change in mental status in hospitalized patient is delirium until proven otherwise

Diagnosis: gold standard is bedside assessment using DSM-5 delirium criteria; disturbance in attention and

awareness; disturbance develops over a short time; represents acute change from baseline attention and awareness; tends to fluctuate in severity during day; additional disturbance in cognition (not just memory deficit, but also visuospatial abilities, executive functioning, language, orientation); disturbances not better explained by pre-existing or established or evolving neurocognitive disorder; does not occur in context of a severely reduced level of arousal such as coma; disturbance is direct physiological consequence of another medical condition, substance intoxication, or withdrawal; main change from DSM-4 to DSM-5 is exclusion of patients with severely reduced arousal; "level of consciousness" term removed from DSM-5, replaced by "awareness," to avoid confusion between delirium and coma (deeper state of sedation than decreased level of alertness in delirium)

Screening and assessment skills: Confusion Assessment Methods — ICU (CAM-ICU), and Nursing Delirium Screening Scale most commonly used; Memorial Delirium Assessment Scale (MDAS) not used in Memorial Sloan Kettering because developed to be used by psychiatrists or experts in delirium to assess severity of (not diagnose) delirium; Single Question in Delirium is screening tool: ask a caregiver or a family member, "Do you feel that your loved one is more confused lately?" if yes, patient likely to be delirious; preliminary study of Single Question in Delirium in patients demonstrated a sensitivity of 80% and a negative predictive value of 91% (psychiatrist interview was reference)

Core symptoms: 97% have attentional deficits; more than 90% have sleep/wake cycle disturbances (not part of DSM-5); 80% have disorientation (20% DO NOT have orientation disturbances; if suspect delirium, ask more than just orientation questions); 80% have memory deficits; 50% have affective changes (depressed, irritable, anxious, or disinhibited); 40% have perceptual disturbances of hallucinations or delusions (60% DO NOT have delusions or hallucinations); 60% have motor agitation; 60% to 70% have motor slowing (mixed psychomotor disturbances possible); subtypes based on psychomotor behavior (hyperactive, hypoactive, or mixed); hypoactive most common but less likely to be recognized; left alone, quietly confused; morbidity and mortality same for all subtypes

Delirium versus dementia: delirium is abrupt and fluctuates during day; dementia has insidious onset; dementia with Lewy bodies may have fluctuations, other dementias have fluctuations only in very final stages; level of consciousness usually impaired in patients with delirium (hypo-alert/hypo-aware or hyper-alert, especially in alcohol or benzodiazepine withdrawal) but not dementia; attention impaired in delirium and may or may not be impaired in dementia; memory can be impaired in both; in delirium, hallucinations and delusions usually scattered, disorganized, and incoherent; paranoid and more detailed in dementia; not all with delirium/dementia have perceptual disturbances or delusions

Delirium versus depression: patients with delirium may be hypo-alert or hyper-alert; patients with depression have no change in level of alertness/awareness; both can have cognitive deficits (mild with depression and more severe with delirium); perceptual disturbances more visual in delirium; patients with depression can have auditory hallucinations (rare); non-systematized delusions in delirium; mood-congruent delusions in depression; patients with delirium may verbalize suicidal ideation as part of disinhibition and lability and should be assessed and monitored for risk of self-harm because could lead to impulsive behavior; in depression, there is hopelessness, guilt, and suicidal, usually with a history of depression; patients with delirium may have history of delirium (always ask about this in history)

Assessment of delirium: young, healthy patients do not easily become delirious; 80-year-old with multiple medical comorbidities may get delirious with a mild urinary tract infection; risk factors are advanced age, dementia, history of delirium, multiple medical comorbidities, severe medical illness, sensory impairment (visual or hearing), increased functional dependency, immobility, history of falls (last 6 months), pain, increased white matter pathology on brain imaging, dehydration, malnutrition (thiamine deficiency); polypharmacy, use of restraints; catheterization; treat as medical emergency; history very important to determine baseline cognitive function; review of systems; medications; alcohol/drug use; pain assessment; vital sign monitoring; physical and neurologic exam; diagnostic workup; specific tests guided by history and exam; chemistry, LFTs, CBC, and TSH; if concern for seizures, obtain EEG; multiple etiologies (any acute medical or surgical change); 3 main etiologies are medications, electrolyte disturbances, and infections

Delirium pathophysiology: inflammatory hypothesis most widely accepted; several neurotransmitter abnormalities in patients with delirium; best-established are cholinesterase inhibition and dopamine activation; thus, it makes sense to use medications that reduce dopamine levels; do not use medications that increase cholinergic activity (study using cholinesterase inhibitors halted because increased risk of mortality); some patients develop delirium and never return to baseline; big debate in psychiatry/neurology whether delirium is a marker of frailty in older adults or if delirium itself leads to dementia; delirium episode can signal vulnerability of brain with decreased cognitive reserve and increased risk of future dementia; growing evidence that delirium causes permanent cognitive impairment and dementia; delirium accelerates cognitive decline; studies show that patients with ICU delirium can still have cognitive dysfunction 3 to 12 months later; long-term cognitive declines after delirium are worse with increased duration and severity of delirium, with the hypo-active type, and in patients with pre-existing dementia or depression

Prevention of delirium: multi-component non-pharmacological interventions reduce incidence in general geriatric medicine by 30%; best single component interventions are reducing sedation and early mobilization in ICU and post-op settings; multi-component interventions do not reduce incidence in advanced cancer in hospice; allow for maximum period of uninterrupted sleep, reduce polypharmacy, facilitate early mobilization, compensate for any sensory losses, encourage oral hydration, monitor nutritional intake, and orient patient; pharmacologic interventions cannot prevent delirium; mixed results in surgical and ICU settings; anti-psychotics, cholinesterase inhibitors, dexmedetomidine, and melatonin have been studied; weak evidence to support melatonin

or melatonin agonists (ramelteon) among older adults in general medical settings; melatonin or melatonin agonist preferred for prevention, because will not cause harm and may reduce delirium incidence; do not use medication that puts patients at higher risk; dexmedetomidine (alpha-2 agonist used in ICU) may reduce incidence of delirium compared with lorazepam, midazolam, propofol

Treatment of delirium: simultaneous identification and elimination of contributing factors; non-pharmacological interventions; medications to treat symptoms if necessary

Non-pharmacological interventions: address cognitive impairment, orient patient, avoid dehydration and constipation, assess for hypoxia, find and treat infections, address mobility and immobility, assess pain, reviewing medications, provide good nutrition, address sensory impairment, and promote good sleep

Pharmacologic management: challenging; primary goal to do no harm; no FDA-approved medications; anti-psychotics, cholinesterase inhibitors, and alpha-2 agonists most frequently used; current evidence supports short-term low-dose anti-psychotics to treat symptoms, with close monitoring, especially in older adults with multiple comorbidities; medication for severe agitation that places patient or others at risk and interferes with patient care; despite risks of anti-psychotics, insufficient evidence to support use of any other psychotropic medication; use very low doses for short times; re-assess for continued need; stop medications once delirium resolves; FDA black box warning for increased risk of death with anti-psychotics in elderly patients with dementia-related psychosis; obtain EKG at baseline and at dose increases (especially of IV anti-psychotics) to monitor for QT prolongation; monitor for extrapyramidal side effects, changes in vital signs; dexmedetomidine used frequently in critical care for symptoms of delirium (some evidence); no evidence to support use of cholinesterase inhibitors (study stopped due to increased mortality risk); psychostimulants used to treat hypo-active type; consider risk of worsening delirium

Post-delirium follow-up: to assess and eliminate predisposing or perpetuating risk factors to prevent future episodes and long-term adverse outcomes; monitor cognitive symptoms after episode resolution; consider cognitive, functional, and physical rehabilitation to prevent adverse outcomes

Assessment of decision-making capacity: any attending physician or nurse practitioner can do an initial assessment (New York State); if there are questions about capacity assessment, or if person completing initial assessment is unsure, can request second person to present concurring opinion; also need concurring opinion if decision involves withdrawing or withholding life-sustaining treatment or if lack of capacity is due to mental illness (not dementia); having a mental illness or cognitive disturbance does not rule out capacity; capacity decisions are time and decision-specific; for example, there may be a patient with a diagnosis of dementia and decision regarding insertion of a Foley catheter, assessment of that decision may not require as high standards as for a decision regarding cardiac surgery; capacity assessed based on risks and benefits of proposed intervention; capacity assessments also time-specific; for example, patient with delirium may lack capacity at time of assessment for a certain treatment, but after the delirium resolves, that person is likely to resume capacity; include reason for lacking capacity and opinion regarding reversibility of condition; four requirements of decision-making capacity: 1) understanding relevant information that is presented, 2) appreciating current situation and its consequences, 3) manipulating information rationally, and 4) communicating a consistent choice; structured scales can be used to assess decision-making capacity; MacArthur Capacity Assessment Test developed to assess decision-making capacity structurally; note that competence and capacity two different things; competence is decision made in court by a judge, not a psychiatrist or other clinician; capacity assessments based on best clinical abilities and specific decisions and are time-limited

Case: What is differential diagnosis for Mr. Hamilton? labs show increased BUN and creatinine, concern for acute kidney injury, hyponatremia; increased white cell count; hypertension; patient has delirium; assessment will include history, physical, neurologic exam, labs, vital signs; patient may or may not need imaging; needs hospitalization; does he have capacity to refuse hospitalization? patient likely lacks capacity to make decision, because it is clear that he needs hospitalization and he is refusing hospitalization; his wife is his next of kin or he may have surrogate healthcare agent; how would you manage this patient? correct underlying etiologies, search for other etiologies and treat, implement non-pharmacologic interventions; if patient is a risk to self or others or has significantly disturbing symptoms, consider medications

Suggested Reading

Abraha I et al: Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. *BMJ Open.* 2017 Mar;7(3):e012759; **Barton W et al:** Assessment of healthcare decision-making capacity. *Arch Clin Neuropsychol* 2016 Sep;31(6):530-40; **Inouye SK et al:** Delirium in elderly people. *Lancet* 2014 Mar;383(9920):911-22.

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Personality Disorders in the Medical Setting

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Introduction: per Michael Stone, "a personality is an aggregate of the ways in which we habitually, predictably, and enduringly relate to others"; personality disorder more specific and different because it implies maladaptation; *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), diagnostic manual for psychiatrists

DSM-5 definition of personality disorder: essential feature of personality disorder, enduring pattern of inner experience and behavior that deviates markedly from expectations of individual's culture; must manifest ≥2 of following areas: cognition, affectivity, interpersonal functioning, impulsive control

- History: many editions of DSM since first published in 1952; most recent edition DSM-5, published in 2013; personality disorders have always been included; *multiaxial system* — in 1980 in DSM-III, personality disorders given diagnostic criteria; multiaxial diagnostic system included in manual, personality disorders coded on Axis II; many people think of personality disorders as Axis II conditions or diagnoses; multiaxial system discontinued in the DSM-5; Axis II no longer appropriate designation
- Age and diagnosis: no age limits for personality disorder diagnoses, except for antisocial personality disorder; individuals with antisocial personality disorder diagnosis must be aged ≥18 yrs; in those aged <18 yrs, features must have been present for ≥1 yr; personality disorders represent long-term functioning. not limited to episodes of illness
- Clusters: DSM-5 organizes 10 personality disorders into 3 clusters based on descriptive similarity
  - Cluster A (eccentric cluster): paranoid personality disorder, schizoid personality disorder, and schizotypal personality disorder; these patients could be problematic in medical setting because of their suspiciousness and distrust
  - Cluster B (dramatic disorder cluster): antisocial personality disorder, borderline personality disorder, histrionic personality disorder, and narcissistic personality disorder; these patients could be problematic because of their tendency to be demanding, to act out, or to be threatening to doctors and staff
  - Cluster C (anxious cluster): avoidant personality disorder, dependent personality disorder, and obsessive-compulsive personality disorder; these patients probably less challenging to physicians because people generally anxious and dependent; they tend to seek approval of others
- Distinction from the general population: abnormal personality traits very common, but people not diagnosed with personality disorder unless these traits inflexible, maladaptive, persisting, and cause significant impairment or distress
- Interactions: different personality disorders tend to overlap and intertwine; most patients with personality disorder tend to have mixture of traits, not just traits of single disorder

Best-validated disorders: 3 disorders best validated of 10 DSM5 personality disorders; each potentially problematic in medical setting

- Schizotypal personality disorder: eccentric cluster; individuals tend to be characterized by eccentricity, odd affect, and psychotic-like symptoms; magical thinking common; tend to be socially isolated; more common in men than in women; tends to be genetically linked with schizophrenia; considered part of the schizophrenia spectrum of disorders; people with this disorder could benefit from low-dose antipsychotic medication; no medication FDA approved; treatment considered off-label
- Antisocial personality disorder: probably most problematic; characterized by pervasive pattern of violation of rights of others; associated with criminality, anger, irritability, and lack of guilt or empathy; most antisocial individuals male; common in prison populations; high heritability; no standard treatment; in severe cases, antipsychotics could be used to dampen anger and hostility; person would have to be willing to take the medication; any use off-label
- Borderline personality disorder: disorder of emotional regulation; symptoms include emotional instability and stormy lifestyle; suicidality and self-harm; tends to begin in late teens or early 20s; most persons with this disorder female; like other personality disorders, high heritability; treatment of choice psychotherapy (specific programs have been developed); could benefit from medication, including antidepressants, mood stabilizers, or antipsychotics; use off-label; no FDA approved indications for medication in borderline personality disorder

Diagnosis and Assessment

Introduction: in medical settings, personality disorders tend to be ignored and likely to go undiagnosed or misdiagnosed; probably due to clinician's unfamiliarity with personality disorders; personality disorder patients more likely than others to seek medical care and even to be hospitalized; also more likely than others to report emotional pain, and somatic-related complaints; people with personality disorders often have little insight or

awareness to their personality problems, or how their traits keep getting them into trouble

Reasons for concern about possible personality disorder: problems that should probably raise concerns include unsubstantiated somatic complaints, unspecified depression or anxiety complaints, pain-related complaints; more problematic, seeking of pain medications, stimulants, or benzodiazepines

Behaviors that may raise suspicions: angry outbursts or verbal threats, sexually provocative behavior, special requests, poor treatment compliance (*eg*, refusing treatment, pulling out tubes or IVs), or pain reported in excess of what would be expected; some patients will elicit very strong emotional reactions from the physician, who understandably gets upset, or even angry with patient

Effect on providing care: presence of personality disorder can interfere with goal of providing good care; many physicians express frustration because of patient's refusal to follow treatment recommendations; understandable if patient seems to sabotage treatment, express anger or hostility, or exhibit unacceptable behavior (*eg*, making threats or insulting staff members); most physicians don't know how to respond well to acting-out patient or how to go about changing patient's behavior; not all people with personality disorder seen in medical settings problematic; obsessive-compulsive personality disorder patient may actually be more compliant than other types of patients and less troublesome overall

Comorbidity: very common; *personality disorders highly unlikely to occur in isolation without 1 of these other conditions present* — mood disorder (*eg*, depression); anxiety disorder (*eg*, panic disorder); trauma-related disorders (*eg*, posttraumatic stress disorder [PTSD]); obsessive-compulsive–related disorders (*eg*, obsessive-compulsive disorder); eating disorders; substance-use disorders; likely that physicians of all types will encounter patients with personality disorder

Epidemiology

Introduction: lifetime prevalence of personality disorders in community probably hovers between 10% and 15%; higher prevalence in special populations; 30% to 50% of patients in hospital and clinic populations; ≤80% of patients in correctional settings (particularly antisocial personality disorder); ≤60% of patients in substance-abusing populations; estimated one-fourth of homeless population has personality disorder

Sex: the prevalence of borderline personality, histrionic personality, and dependent personality higher in women; antisocial personality disorder more common in men

Clusters: in surveys, most frequent personality disorders tend to be those in cluster C (shy, anxious, or dependent individuals); cluster B disorders less frequent but more problematic because of acting-out behavior such as that found in people with antisocial personality disorder or borderline personality disorder; cluster A disorders (eccentric cluster) tend to be less common but can be source of difficulty, particularly if person paranoid or suspicious

Characteristics of Personality Disorders

Introduction: probably best considered as pathologic exaggerations of traits amplified through interactions between genetic predisposition, psychosocial stressors, and social factors; ≥3 most valid conditions have high heritability; genes convey vulnerability while environment and life stressors promote clinical expression of that vulnerability

Chronicity: often considered chronic and enduring; designation included in DSM; most personality disorders tend to be diagnosed more commonly in younger populations, especially people aged between 25 and 44 yrs; follow-up data actually show that personality disorders not as stable as people might think; follow-up studies of people with personality disorders show that many will no longer meet diagnostic criteria over time; important to remember that even though they don't meet formal criteria, most will continue to have emotional and psychosocial problems that relate to their personality disorder

Response to stressors: tend to wax and wane in severity in response to stressors (*eg*, hospitalization or illness) or in response to depression or anxiety; if person hospitalized or depressed, traits may be more prominent

Elderly individuals: personality disorders occur even in elderly persons; tend to be less common; personality disorder may have improved or subsided over time; in follow-up studies, many persons who would have met criteria for personality disorder deceased and not available for follow-up; older people with personality disorders tend to be less impulsive than their younger counterparts; exhibit less self-harm, have fewer suicide attempts, and tend to be psychiatrically hospitalized less often; if you see an older adult with a presumed personality disorder, you need to look for medical explanations, particularly if maladaptive traits relatively new and not typical for that person; consider tumor, stroke, dementing illness

Recognition of Personality Disorders

Introduction: psychiatrists can assess in detail; internists and other generalists probably don't ask about symptoms suggestive of personality disorder; if they see someone with emotional or psychiatric problems, they probably focus on immediate complaint (*eg*, depression or anxiety); perhaps person has simply come in and presented for medical complaint, which doctor focuses on

Recognition: person should be asked about mood stability, interpersonal relationships, sense of self, work history, and ability to control impulses; even reality testing (*eg*, whether or not they have illusions, hallucinations, or something that may sound like that); collateral information helpful in hospital setting; nurses, social workers, visiting family and friends can provide other information

Research setting: structured interviews enhance identification of personality disorders; not generally used by clinicians, although they could be; rating scales available for only few personality disorders; borderline personality disorder probably most heavily studied of 10 personality disorder types; one scale, self-report, quite valid, Borderline Estimate of Severity Over Time (BEST)

Clinical setting: tend to use Zanarini rating scale for borderline personality disorder; can rate severity and change during clinical trial; diagnosis based on pattern recognition; recognize cardinal symptoms

Cardinal symptoms: *schizoid personality disorder* — cluster A; social isolation; *histrionic personality disorder* — cluster B; exaggerated emotionality; *borderline personality disorder* — also cluster B; mood instability and suicidality; *obsessive-compulsive personality disorder* — cluster C; rigidity and perfectionism

Questions to ask: *several simple questions physicians can ask with high likelihood of identifying people with personality disorder* — 1. does patient have days when mood constantly changing? 2. how does patient feel when not center of attention? 3. does patient frequently insist on having what they want right away? 4. is patient concerned that certain friends or coworkers not really loyal or trustworthy? 5. is patient concerned about saying wrong things in front of other people? 6. how often does patient avoid getting to know someone because worry that person may not like the him or her?

Differential diagnosis: broad differential diagnosis for personality disorders that internists and other nonpsychiatric physicians should think about; personality disorder could be confused with psychotic disorder; (*eg*, schizotypal personality disorder, in which person has mild thought disorder or magical thinking that could suggest schizophrenia); anxiety disorders need to be included in differential; consider depressive disorders; also consider PTSD, substance-use disorders, and personality changes from medical disorders (*eg*, tumor, stroke, or brain injury); another possibility to consider in patient thought to possibly have personality disorder, person's behavior actually within normal limits; not all difficult patient behavior indicates presence of personality disorder; patient may be exhibiting normal behavior under those circumstances; nearly all patients regress when in hospital; patients may act out now and then in response to new diagnosis, to facing difficult decisions, or to experiencing pain

Perceptions: many clinicians have negative bias towards those with diagnosis of personality disorder; study from Britain in 1980s showed that, in comparison with other patients, personality disorder patients reported to be more difficult, less deserving of mental health resources, more manipulative and attention seeking, and yet more in control of suicidal and self-harm urges than others; those results still hold up; more recent study of patients with borderline personality disorder showed disturbing findings; result of survey at 9 academic medical centers; involved 706 clinicians asked variety of questions about borderline personality disorder; 47% said they preferred to avoid caring for those patients

Management

Introduction: important to note presence of personality disorder; people with personality disorders tend to have worse health care outcomes; patients with personality disorders more likely to have history of domestic violence and physical, emotional, and sexual abuse; more likely to be unemployed or homeless, to exhibit criminality and have history of incarceration, to abuse substances, to suffer traumatic accidents, and to commit suicide; have increased health care utilization; more likely to end up in emergency departments, clinics, and hospitals than other people

Managing difficult or disruptive patients: first thing physicians need to do, understand their own emotions and to try to put their feelings aside; for example, patient on inpatient unit who may be disruptive, or yelling, or pulling tubes out, tends to upset physicians; they may be tempted to yell at patient or talk back to them; have to learn to put feelings aside; need to have empathy and offer support to patient; need to try to get sense of the patient and his or her source of distress; being in hospital can lead people to acting out more than they otherwise would; in short term, may help to try to give patient sense of control; for example, allow patient to make at least simple decisions involving care and to be involved in major decisions; sometimes people feel excluded from that; physician and team members need to be consistent in their care of this patient; minimize changes in treatment plans; set limits; not inappropriate to let patient know when his or her behavior unacceptable; manage staff splitting by getting all staff on board (some patients will try to split staff into group of people considered enemies and then those on patient's side); all team members need to be on the same page

Response to suspected or diagnosed personality disorder: if patient out of control and needs to be calmed, can offer tranquilizing medication (eg, second-generation antipsychotic or antihistamine); avoid benzodiazepines because they could further disinhibit patient; cannot force patient to take medication in absence of court order; patient may reject that

Treatment: medication unlikely to be important part of intervention; much of intervention probably needs to be behavioral; seek consultation from psychiatrists who regularly deal with such patients; any large hospital will have psychiatric consult liaison team; in making referral, be specific about problem leading up to consultation; regarding long-term management, internists and other physicians need to understand no quick fixes exist for these patients; at least in hospital setting, lecturer divides his understanding of management into acute, or short-term, and then long-term care; acute, or short-term, care includes medication and behavioral suggestions; long-term interventions consultant might recommend include psychotherapy and perhaps medication; if substance-use disorder suspected or diagnosed, that needs to be managed because personality disorders tend to be much worse and more severe in presence of active substance abuse; all physicians should understand that some types of personality disorders respond better than others; no evidence-based treatments for antisocial personality disorder

Borderline personality disorder: specific treatment approaches evidenced based and effective; best-studied personality disorder; evidence-based programs involve either individual or group psychotherapy, sometimes both; dialectical behavior therapy used since early 1990s and best-established mentalizing therapy; other approaches include transference-focused psychotherapy, schema-focused therapy, and systems training for emotional predictability and problem solving (STEPS); effective, but have limited availability; psychiatric consultant will be able to refer patient to therapy available within physician's area

Medication: no FDA-approved medications for any personality disorder; no general guidelines for use of medication; evidence suggests that antidepressants, mood stabilizers, and second-generation antipsychotics

can be helpful and reduce symptoms associated with borderline personality disorder (but they don't change fundamental problem); medication should be targeted at comorbid disorder if present; could target medication at major depressive disorder, panic disorder, or other condition; sometimes medication should be targeted at preponderant problematic symptom (*eg*, anger or hostility); no FDA-approved medications to treat anger and hostility, but second-generation antipsychotics seem to reduce anger, irritability, and hostility in off-label use

Cautions: avoid older medications (*eg*, tricyclic antidepressants or monoamine oxidase inhibitors) because possibly lethal in overdose; many personality disorder patients impulsive; may attempt suicide (borderline personality disorder patients often have that history); we know from studies that about three-fourths of those patients will attempt suicide at some point during their lifetime; avoid benzodiazepines because they can lead to addiction and may contribute to acting-out behavior from disinhibition

Suggested Reading

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Mood, Anxiety, and Psychotic Disorders in the Medical Setting

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Introduction: mood and anxiety disorders prevalent in medical settings; patients may report symptoms of depression or anxiety or seek treatment for those conditions; physicians may pick up symptoms during routine care of patients when seen for medical problems; mood or anxiety disorder may become apparent by interfering with or disrupting medical care; psychotic disorders less common but found in many patients seeking medical care; patient may not describe psychosis or appear particularly odd or abnormal; then again, psychosis could be obvious and disruptive in medical setting and to care of individual; internists and other generalists need understand these disorders and their clinical management even if not charged with care of those patients; fairly easy to incorporate simple questions into patient visit to identify and even diagnose some of these disorders

Assessment: be alert to patient's appearance and affect; note if patient appears depressed; note if person seems to feel too good or even high; note if patient's affect blunted or giddy; note if any evidence of psychomotor retardation or agitation; ask about mood (has patient been sad or blue? has patient felt too good or even high? has patient had thoughts about death or dying, or even of taking their life?); some mood patients have psychotic features, so possibly incorporate questions about that; maybe ask if patient has ever heard voices or seen things that others can't, or if patient has been very paranoid or suspicious

Diagnostic and Statistical Manual of Mental Disorders, 5th Edition **(DSM-5):** DSM-5 psychiatrist's diagnostic manual; lists all recognized disorders

DSM-5 Mood Disorders

Mood disorders: chapter on bipolar disorders includes of bipolar 1 disorder, bipolar 2 disorder, and cyclothymia; another chapter covers depressive disorders and includes discussions of major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, and new diagnosis, disruptive mood dysregulation disorder; other conditions also involve depressive symptoms, *eg*, bereavement (bereavement itself not considered mental disorder, but can cause significant pain and come to doctor's attention) and adjustment disorder with depressed mood (some patients have trouble adjusting to some life change or stressor and develop depression as result; common in hospital setting)

Bipolar disorders: includes bipolar 1 disorder, bipolar 2 disorder, and cyclothymia; also substance- or medication- induced bipolar disorder and bipolar disorder due to another medical disorder (*eg*, stroke or brain injury)

Bipolar 1 disorder: criteria specify that person meet criteria for manic disorder at least once during life; patients generally experience episodes of mania and depression; may have more manic episodes early in course; may experience more depressive episodes as they grow older

Mania: to diagnose, must be distinct period of abnormally and persistently elevated expansive or irritable mood lasting ≥1 wk; *must exhibit ≥3 of these 7 symptoms* — inflated self-esteem or grandiosity; decreased need for sleep; being more talkative or exhibiting pressured speech; exhibiting flight of ideas or expressing feeling that they have racing thoughts; distractibility; increase in goal-directed activity or psychomotor agitation; excessive involvement in activities with potential for painful consequences (*eg*, new business, romantic affair); symptoms must cause marked impairment; symptoms must not be due to effects of substance or another medical condition; mania tends to be obvious and may be disruptive; family members may feel exhausted from caring for their loved one and seek help; patient typically has little insight and feels well; patient will often say best they've ever felt, nothing wrong with them; some patients have psychotic features, generally mood-congruent psychotic features

Bipolar 2 disorder: much milder; episodes of depression and ≥1 period of hypomania (milder and briefer form of mania); periods of hypomania generally occur before or after depressive spells; not accompanied by psychotic symptoms; hypomania typically does not lead to hospitalization, unlike bipolar 1 disorder and manic episodes; high rates of comorbid substance abuse; people with bipolar 2 disorder often develop chronic mild depression

Cyclothymia: mild mood swings between poles of depression and hypomania; for diagnosis, condition must have lasted ≥2 yrs, with hypomanic episodes interspersed with mild depressions that fail to meet criteria for major depression; diagnosis rarely used by psychiatrists

Epidemiology and course of bipolar 1 and 2 disorders: approximately 2% lifetime prevalence of bipolar 1 and 2 combined; more common in women (~3:2 ratio); potential for real-life impairment and diminished quality of life, particularly with bipolar 1 disorder; can consist of marital discord, impaired decision making, drug and alcohol abuse; ~10% of bipolar patients will eventually commit suicide, usually during phase characterized by mixed symptoms or predominantly depression; comorbidity common (*eg*, anxiety disorders, substance use disorders, personality disorders); bipolar 1 disorder

generally has mean age of onset ~25 years, onset can be abrupt; episodes of mania can last wks or mos; high recurrence rate; many people with bipolar disorder end up with chronic mood instability; chronic symptoms in between episodes; person may have more episodes of depression than mania as he or she ages

- Characteristics of mania: symptoms include elated mood and/or grandiosity; some patients may claim best they've ever felt or feel on top of world; often exhibit rapid and pressured speech; may be difficult to interrupt and will talk as long as allowed; exhibit increased energy or activity, increased libido; often say sex drive high, which may have contributed to engaging in sexual relationship outside marriage; feel they have increased cognitive speed; feel smarter and thinking faster; often accompanied by impaired decision making; some patients have psychotic symptoms, mostly mood-congruent delusions; grandiose and religious themes common
- Differential diagnoses: schizophrenia (characterized by psychotic features); schizoaffective disorder (consists of mixture of mood and psychotic disorders); substance-induced mania (*eg*, stimulant medications can induce manic-like state); must rule out possibility of mania from another medical disorder (*eg*, hyperthyroidism)
- Treatment: medication; in severe cases, electroconvulsive therapy (ECT); in both cases, accompanied by supportive psychotherapy; FDA-approved medications include lithium carbonate, valproate, carbamazepine, and lamotrigine (latter 3 anticonvulsants); another class of medications, second-generation antipsychotics; all but clozapine and lurasidone approved to treat acute mania; ECT very effective but because medication effective, rarely need to resort to ECT; all patients can benefit from supportive therapy; doctor should convey interest and support and encourage medication compliance
  - Mechanism of action of mood stabilizers: *lithium* — naturally occurring salt, discovered to be effective in treating mania in 1950s; unclear exactly how it works, but inhibits metabolism of phosphoinositide in many second and third messengers, including G proteins; *valproate* — simple branched-chain carboxylic acid; commonly used as antiepileptic; enhances central nervous system (CNS) levels of gamma-aminobutyric acid (GABA); *carbamazepine* — antiepileptic; has wide range of cellular and intracellular effects in CNS, known to dampen kindling; *lamotrigine* — antiepileptic; blocks sodium channels, inhibiting release of presynaptic glutamate, aspartate, and GABA; generally psychiatrists initially use lithium, carbamazepine, or valproate; monotherapy with second-generation antipsychotic also effective and in combination with mood stabilizer such as lithium, carbamazepine, or valproate, may be even more effective if single agent alone insufficient
  - Treatment with medication: with lithium, aim for blood level of 0.8 mEq/L to 1.2 mEq/L and monitor renal function and thyroid indices; lamotrigine may be particularly effective in preventing episodes of depression; well tolerated, but monitor for rashes that could herald Stevens-Johnson Syndrome; dose must be carefully titrated
  - Role of internist: most bipolar patients under care of psychiatrist; internists should understand diagnosis, what it means, and treatments; may be in position to pick up on undiagnosed patients; those patients should be referred to psychiatrist; those on second-generation antipsychotics may develop metabolic problems and could benefit from dietary advice and monitoring for blood glucose and lipid elevations

Depressive disorders: include major depressive disorder (what most doctors think about when they consider depression); persistent depressive disorder (chronic low-level depression); premenstrual dysphoric disorder (occurs in women during late [luteal] phase of menstruation); disruptive mood dysregulation disorder (entity created to diagnose chronically irritable children); 2 conditions with substantial depressive symptoms not coded as mood disorders include bereavement (occurs in response to death of loved one) and adjustment disorder with depressed mood

- Symptoms of major depressive disorder: *5 of 9 symptoms must be present for ≥2 wks (must include either depressed mood or loss of interest)* — depressed mood; loss of interest or pleasure; weight loss or change in appetite; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or guilt; impaired ability to concentrate; recurrent thoughts of death or dying, suicidal thoughts, or suicide attempts; person must have clinically significant distress or impairment in functioning because of symptoms; must have ruled out that depression resulting from effects of substance or medical condition such (*eg*, hypothyroidism); must rule out that not better accounted for by psychotic disorder (*eg*, schizophrenia); must ascertain that person has never had manic episode (would merit diagnosis of bipolar disorder)
  - Epidemiology and course of illness: major depression quite common; recent study found 17% lifetime prevalence rate in general population; more common in women than in men (2:1 ratio); mean age of onset in early 30s; ~20% of those individuals have psychotic features (*eg*, hallucinations, delusions); depression becomes chronic in ~20%; most of others will have recurrent depression; ~10% to 15% of those with depression severe enough to require hospitalization will eventually commit suicide
- Persistent depressive disorder: chronic low-level depression; quite common; found in ~2% to 3% of adult population
- Mood disorder subtypes: could be used with either mania or depression; *with psychotic features* — for mood patient with delusions or hallucinations; psychotic features characterized as either mood congruent (*ie*, compatible with symptoms that patient presents with), or mood incongruent; *with mixed features* — individuals who display mixture of depressive and manic symptoms; w*ith rapid cycling* — person has had ≥4 mood episodes in past 12 mos; *with catatonic features* — individual with mutism, rigidity, and waxy flexibility; *with seasonal pattern* — person with temporal pattern of mood symptoms that occur at particular time of year (commonly referred to as seasonal affective disorder)
- Symptoms of depression: depressed mood, loss of interest; poor appetite with weight loss, but occasionally

opposite seen; other symptoms include low energy, sleep disturbance, decreased libido, poor concentration or inattention, suicidal thoughts or acts, and anxiety and tension

Differential diagnosis: quite broad; includes schizophrenia, schizoaffective disorder, substance-induced depressive disorder, and depressive disorder due to another medical disorder (*eg*, hypothyroidism)

Comorbidity: common and broad range; includes anxiety disorders (*eg*, panic disorder or social anxiety disorder); somatiform disorders; eating disorders; substance-use disorders; personality disorders; may have trauma-related disorder (*eg*, posttraumatic stress disorder [PTSD]); obsessive-compulsive–related disorder (*eg*, obsessive-compulsive disorder [OCD])

Diagnosis: begins with recognition; could manifest in doctor's office as depressed affect, reports that person sad or blue, *etc*

- Screeners: 2 have come into common use, quite helpful; self-reports (easy to have assistant give these to patient upon entering doctor's office
- Patient Health Questionnaire-2 (PHQ-2); only 2 questions; first relates to loss of interest or pleasure; second relates to depressed mood; each rated between 0 and 3; total score ranges from 0 to 6; patient with score of ≥3 should be further screened; further screening could include Patient Health Questionnaire-9 (PHQ-9)
- PHQ-9: 9 questions corresponding to DSM-5 symptom criteria; each rated between 0 and 3; scores range from 0 to 27; score of ≥5 corresponds to clinical depression; may be repeated over time to monitor patient's progress as depression being treated
- Others: Beck Depression Inventory and Zung Depression Inventory; many others

Treatment: *psychotherapy* — generally for mild cases or used in combination with medication; evidence-based psychotherapies include cognitive behavioral therapy and interpersonal psychotherapy; *medications* — antidepressants, serotonin-specific reuptake inhibitor (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), others; anxiolytics (*eg*, benzodiazepines) often used in combination with antidepressant, particularly if patient has prominent anxiety symptoms; antipsychotics often used as well, either as mood stabilizers or to treat psychotic symptoms that may occur; most psychiatrists now prefer using second-generation over first-generation antipsychotics because well tolerated and effective; *ECT* — reserved for cases of depression not responsive to medication or for certain symptoms (*eg*, catatonic symptoms and psychotic features)

- Antidepressants: most work because they enhance transmission of serotonin, norepinephrine, or both; most about equally effective and work in ~60% to 70% of cases; placebo response rate itself high, (30%-50%); popularity of newer drugs marketed over last 10 yrs to 15 yrs more to do with improved side-effect profile and lower toxicity with overdose, not enhanced response rates
- Approach: most psychiatrists begin with SSRI, SNRI, or another, newer antidepressant because well tolerated; TCAs and MAOIs now used only in treatment-resistant cases and both potentially fatal with overdose; therapeutic effects for antidepressants generally take 2 wks to 4 wks to become apparent, 4 wks to 6 wks or longer for maximum benefit; for those with heart rhythm disturbances, newer antidepressant should be used (*eg*, SSRI, bupropion, mirtazapine)
- Discontinuation: patient coming off SSRI or SNRI should be weaned gradually to avoid withdrawal syndrome (anxiety, jitteriness, nausea, dizziness); fluoxetine self-tapers because metabolized at very long half-life, so can be stopped abruptly
- Practical issues of treatment: patient should be evaluated for suicidal thoughts or plans; if safety issue, patient should be hospitalized; should also be hospitalized if unable to care for him- or herself; medication deemed essential for moderate to severe cases; psychotherapy alone can be effective for mild cases; some patients prefer psychotherapy over medication, and that should be honored; medication plus psychotherapy may be more effective than 1 treatment alone; ECT tends to work best psychotic or catatonic patients or those with acute onset of illness

Role of internist: many cases that internists and other generalists see probably do not require referral to psychiatrist; if patient in mild-to-moderate range, internist can diagnose condition, prescribe antidepressant, and monitor improvement; if patient psychotic or suicidal, case complicated by comorbid disorder, or patient fails to respond to treatment or needs psychotherapy, referral to psychiatrist needed; can easily monitor treatment response with the PHQ-9

Anxiety Disorders

Introduction: to quote from DSM-5, "anxiety is the apprehensive anticipation of future danger of misfortune accompanied by a feeling of worry, distress, and/or somatic symptoms of tension"; focus of anticipated danger may be internal or external

DSM-5 anxiety disorders: separation anxiety disorder and selective mutism (generally diagnosed in children); specific phobia, (fear of specific object or situation); social anxiety disorder (formerly known as social phobia), in which the person has fears of social interactions or engagements; others include panic disorder, agoraphobia, and generalized anxiety disorder; DSM-5 recognizes that substances and medications can induce anxiety disorders, as can medical conditions

Other DSM-5 disorders: some disorders characterized by significant anxiety, but not included in anxiety disorder chapter; these include (has own chapter dealing with OCD and related disorders); PTSD and acute dress disorder found in different chapter on trauma and stressor-related disorders); adjustment disorder with anxiety occurs in response to stressful situation, tends to be temporary, does not rise to level of meeting full diagnosis of some anxiety disorder (*eg*, panic disorder)

Frequency: common in general population, as well as in special settings; ~10% to 15% of patients in primary care setting have anxiety disorder; ~40% of psychiatric outpatients; associated with medical conditions such as cardiovascular disease, respiratory illness, arthritis, and migraine; doctors treating patients for one of those conditions should seek out presence of anxiety disorder; specific phobias perhaps most common (~16%); social

anxiety disorder (~11%); separation anxiety disorder (~6.5%); generalized anxiety disorder (~4%); panic disorder (4%); agoraphobia at (~2.5%); more woman than men meet criteria for anxiety disorder

Course of illness and age of onset: tend to be chronic, but fluctuate in severity and intensity, depending on other factors in person's life; interfere with social and occupational functioning but usually not incapacitating; most psychiatrists consider anxiety disorders outpatient conditions, not something generally requiring hospitalization; age of onset varies; separation anxiety disorder starts at ~7 yrs; social anxiety disorder starts in early teen yrs; panic disorder and agoraphobia start in early 20s; generalized anxiety disorder has later age of onset, usually in early 30s

Symptoms: tension and irritability, feeling restless or keyed up, jitteriness or trembling, fatigue, impaired concentration and attention, panic attacks, fears and phobias

Treatment: fairly similar from 1 disorder to another; focuses on use of antidepressant medications; typically involves combination of medication and psychotherapy; medications either SSRIs or SNRIs; also benzodiazepines, but usually just temporary treatment; may use beta blockers (*eg*, propranolol) or antihistamines, because of tranquilizing effect; cognitive behavioral therapy efficacious; elements include cognitive restructuring, exposure desensitization, relaxation, and rebreathing

Practical issues of treatment: generally considered outpatient problem, but patient should be hospitalized if incapacitated or suicidal; need to rule out substances and medical conditions as cause of anxiety (*eg*, too much caffeine can induce what appears to be anxiety disorder; so can hyperthyroidism and other conditions); mild disorders may respond to simple reassurance from physician, relaxation training, or short-term use of benzodiazepines (*eg*, someone with mild case of social anxiety may benefit from temporary use of benzodiazepine); medication generally indicated in moderate to severe cases of anxiety; buspirone, indicated for generalized anxiety disorder, does not block panic attacks and therefore generally not helpful in anxiety disorders except for generalized anxiety disorder; comorbidity common, so be alert to other disorders, including depression; most patients could benefit from cognitive behavioral therapy

FDA indications for anxiety disorder treatment: *panic disorder* — fluoxetine, paroxetine, and sertraline (SSRIs); venlafaxine (SNRI); benzodiazepines alprazolam and clonazepam; *social anxiety disorder* — paroxetine, sertraline, and venlafaxine; *generalized anxiety disorder* — paroxetine, escitalopram, venlafaxine, duloxetine, and buspirone; much of prescribing for these patients off-label; some other medications used include some newer SNRIs, including desvenlafaxine and milnacipran; TCAs occasionally effective, but not effective in social anxiety disorder; MAOIs effective; sometimes gabapentin and pregabalin used; atypical antipsychotics sometimes used; beta blockers (eg, propranolol) generally effective for social anxiety related to performing in public

Role of internist: can be very helpful; can competently treat mild cases; refer cases to psychiatrists when failure to respond to medication, need for psychotherapy, patient has suicidal thoughts or behaviors, or if case complicated by comorbid disorders; start with low-dose SSRIs; generally takes 4 wks to 6 wks for meaningful response, 12 wks to 16 wks for optimal response; dosing similar to that for depression; if no response, can try another SSRI or SNRI; with panic disorder, goal to have the panic attacks blocked completely (may take some time); TCAs and MAOIs second-line treatments; buspirone does not block panic attacks, so reserve for generalized anxiety disorder; combined treatment with medication and cognitive behavioral therapy probably most effective therapy

Psychotic Disorders

Introduction: *DSM-5 lists the following as psychotic disorders* — schizophreniform disorder, schizophrenia, schizoaffective disorder, delusional disorder, and brief psychotic disorder; all characterized by presence of hallucinations and/or delusions

Schizophrenia: most important; prevalence of about ~0.5% to 1% of general population; more men than women diagnosed with schizophrenia; onset in the late teens or early 20s, tends to be earlier in men than in women; for most people, chronic and lifelong; can be totally disabling; ~10% of these individuals eventually commit suicide; comorbidity common, particularly substance abuse with tobacco, alcohol, and other drugs

Symptoms: broken down into positive symptoms, negative symptoms, and disorganization; positive symptoms include hallucinations (can be auditory, visual, olfactory, or tactile); another positive symptom, presence of delusions or fixed false beliefs; most common tend to be paranoid delusions in which person being persecuted; negative symptoms include lack of motivation, flat affect, asociality, and anhedonia (lack of ability to experience pleasure); disorganization includes disorganized speech (thought disorder), disorganized behavior, and inappropriate affect (eg, laughing when being told of something very sad)

Treatment: includes use of antipsychotic medications; first-generation antipsychotics include haloperidol; tend to have a high propensity for extrapyramidal side effects (*eg*, pseudo-Parkinsonism); second-generation antipsychotics tend to be better tolerated; less likely to cause extrapyramidal symptoms but more likely to induce metabolic symptoms including weight gain and prediabetes; monitor metabolic parameters (*eg*, weight, serum lipids, serum glucose)

Psychosocial approaches: important in treating these patients; could include enrollment in day treatment program, partial hospital program, or assertive community treatment in which mobile health care teams go to person's home on regular basis to check them, provide medication, and give advice; many of these patients disabled, and part of doctor's role to help them obtain disability benefits or to help with housing; psychiatrists work closely with social workers

Practical issues: because suicide eventual outcome for many, need to be carefully evaluated for presence of suicidal thoughts, behaviors, or plans; if patient suicidal, should probably be hospitalized to ensure safety; some patients will become homicidal towards others, so would need to be hospitalized; many unable

to care for themselves, so need hospitalization and eventually placement in care facility or nursing home; need to be treated aggressively with antipsychotic medication; ECT rarely used but can be effective in catatonic forms of schizophrenia or if schizophrenic patient severely depressed; may benefit from concurrent antidepressant or mood-stabilizing medication, though data are limited; may need help in obtaining disability benefits or housing

Role of internist: can help by identifying new cases; if new cases picked up, patient should be referred to psychiatrist; if patient diagnosed and on second-generation ant-psychotic, internist can help by monitoring metabolic side effects

Suggested Reading

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Addiction Medicine: Core Knowledge and Skills for Medical Clinicians

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Overview: important for all clinicians, as substance use disorders are frequently encountered in inpatient and outpatient medical settings; contributing factors in a wide range of medical and psychiatric complaints, not just those often associated with substance use like liver disease with heavy alcohol use, but also a wide range of GI, cardiac, neurologic, traumatic, and behavioral disorders; physical and emotional effects of substance abuse can be dramatic; often not apparent unless looked for; interventions and treatments have demonstrated effectiveness, rates of compliance and success similar to many chronic diseases

Perspective: though recent public attention has focused on abuse and overdose related to opioids and generally often has focused mainly on illegal drugs, most of the morbidity and mortality from substance use is secondary to alcohol and tobacco use; in the US, nicotine use and dependence are estimated to be responsible for up to 400,000 deaths per year and alcohol for at least 100,000 deaths per year; opioids and cocaine combined account for approximately one-tenth that number, which still represents over 50,000 individuals; though current epidemic of opioid misuse and overuse of benzodiazepines must be addressed, one should not lose sight of the problems caused by two drugs that are legal, readily available, heavily promoted, and tolerated by the culture at large

Reasons for problem use: most people who use drugs use them infrequently or at low risk; a smaller but significant number use more heavily or in risky situations; relatively small percentage become addicted; generally true for alcohol, opioid analgesics, cocaine, or cannabis; this continuum of substance use disorders often represented graphically as a pyramid with the most numerous, low-risk, non-problematic users at the base, addicts at the narrow peak, and the higher risk or problematic non-addicted users filling significant parts of the middle; their problem is not as serious, but their number is much greater; a clinician who is conscientiously screening and evaluating for substance use disorders will most often identify low-risk users; this provides multiple opportunities for prevention messages for low-risk users, and for brief but potentially effective interventions for those at risk but not yet out of control; that group accounts for majority of public health impact

Terminology: disorders traditionally called alcoholism and drug addiction, individuals called alcoholics or addicts; seen as all or none, as a moral failing or character weakness; in 1980s and '90s, drug abuse or dependence became accepted terms, suggesting the continuum model; trend furthered in 2013 by the DSM-5 (Diagnostic and Statistical Manual, Fifth Edition) terminology mild, moderate, or severe substance use disorder

Advantages: these diagnostic changes eliminate potentially confusing terms like abuse and dependence and make clear that there is a range of disorders; treatment should not be all or none; should be tailored to level of disorder

Risk factors: some individuals are at greater risk than others to progress to problematic or out-of-control use; many theories about why some people are affected differently from others; moral model still exists, but public health model is more useful in relation to risk, progression, and recovery; posits that disease develops as interaction between a host, a particular agent, and the environment; risk factors for substance disorders have been identified; genetics plays a role, particularly for sons of addicted fathers; so do character factors like impulsivity and risk taking, a pronounced response to or tolerance for a drug's effects, and early age of first use; notable increase in risk from mental health conditions such as mood disorders and from trauma and chronic pain

Mental health-related risk: most directly demonstrated by the direct association between individual's number of adverse childhood events (ACE score) and risk of substance use disorders later; reinforces importance of environmental variables, including cultural factors such as drug availability, peer attitudes, social sanctions or rewards, availability of role models, jobs, or other social resources, any of which can increase or mitigate risk

Characteristics of drugs: can enhance or lessen abuse potential; examples include rate of onset, duration of action, and intensity or rewarding character of the effect, whether euphoria, sedation, stimulation, or stupor; how these characteristics interact with a particular host's nervous system and emotional and physical needs is critical; effects pleasurable for some are irritating to others; intensity of reward and ability to tolerate side effects can lead some to repeated or regular use; developing tolerance to pleasurable effects can also lead to increasing use

Patterns of use: as some individuals progress to using more regularly and more heavily, they find use becoming more prominent in their lives; expands into more aspects of life; other behavioral options atrophy; as problems develop, will tend to avoid seeing the connection with the drug; even when problems are recognized, will continue to use; use has become less volitional and

more compulsive; potentially on the way to being out of control

Prescription drugs: process can be subtle with prescription drugs like opioids or benzodiazepines; patient may see use as validated by the fact of prescription, regardless of risks or problems; may dismiss problems; drug seen as only way to manage pain or deal with stress or anxiety

Worsening use: with continued regular heavy drug use, whether of alcohol, nicotine, opioids, benzodiazepines, or cannabis, neuroadaptation progresses in core primitive reward and attention systems of brain like limbic and hippocampal systems; drug becomes necessary to maintain function and sense of well-being; guiding or restraining force of frontal cortex circuits is increasingly impaired, lessening ability to resist impulse to use; individual has become less of a volitional user; use has become less about getting high, and more about maintenance of habit; leads towards being out of control; meets many or most DSM-5 criteria for substance use disorder

DSM-5 substance use disorder criteria: individual reports or demonstrates tolerance, possible physical dependence, and withdrawal, craving, or a strong desire to use; taking drug in larger amounts or over a longer period of time than intended; wanting to control, cut down, or quit use but being unable to do so; spending a great deal of time in obtaining and using the substance; recurrently using substance in physically hazardous situations; giving up or reducing important activities; continuing to use despite interpersonal, emotional, or physical problems; number of positive responses to these criteria will place the individual diagnostically at a point somewhere on the substance use disorder continuum; less than four equals mild substance use disorder; four or five equals moderate, and six or more indicates severe substance use disorder that was traditionally called addiction

Commonly abused drugs: how and why used, potential complications, presentation in medical system

Sedatives, depressants, and alcohol: although alcohol can have stimulating properties, particularly early in intoxication, is in class of sedatives and depressants, which includes benzodiazepines and sleep aids like zolpidem, as well as barbiturates; before advent of benzodiazepines, barbiturates were major category of abused medication; currently, butalbital, an ingredient in headache medicine Fioricet, is most commonly abused, as well as meprobamate, a barbiturate-like drug previously marketed as Miltown; it is in Equagesic and also the primary active metabolite in carisoprodol, the muscle relaxant Soma

Use and effects: commonly taken by mouth, benzodiazepines and barbiturates can also be injected; used for variety of reasons, ranging from intoxication, sedation, decreasing anxiety, and decreasing inhibition; often used in combination to maximize effect; used to take edge off side effects from stimulating drugs like cocaine or to help user come down from binge; main complications of this class are direct results of cognitive clouding, sedation, and psychomotor impairment; these, along with impaired judgment, impulsiveness, and disinhibition, lead to accidents, trauma, STDs, and a host of emotional and interpersonal consequences; dependence may develop in an attempt to self-medicate for conditions such as anxiety, agitation, or withdrawal; tends to make these symptoms worse rather than better over time

Alcohol: has the complication of being metabolically toxic to a number of organ systems; medical complications are numerous, ranging from irritating to catastrophic; toxic effects on liver, stomach, and pancreas; potentially toxic to cardiovascular system, central and peripheral nervous systems, endocrine function, and sexual function; overuse can be a primary or contributing cause of hypertension, dysrhythmia, mild to severe gastric disorders, neuropathy, cognitive decline, erectile dysfunction, and full range of depression and other mood disorders; physical dependence and withdrawal is a significant concern with this class because it can be serious; includes seizures as well as delirium; carries mortality risk; risk of overdose, either alone or in combination, particularly with opioids

Tobacco and nicotine: risks and consequences are well known; newest development is the wider availability of e-cigarettes or vapes; thought to avoid some of the risks, but come with concerns about risk of increasing nicotine availability and dependence as well as unidentified risks associated with device components; nicotine products are most commonly smoked; smokeless alternatives like dip or chew carry risk of dependency and significant health risks; effect of nicotine is mixture of activation and calm, both by direct effect and by alleviation of withdrawal and craving; problems include cardiovascular and pulmonary risks; risks of carcinogenesis, and perinatal complications

Cannabinoids: most commonly used illegal class of drugs, with recent increased legal availability in many states; products include marijuana, hash, hash oil, and recently a variety of edible products; typically smoked; can be eaten; used for euphoria and altered or enhanced sensation; may elicit activation and increased sociability; for others, are calming or sedating; use for pain relief now has support from research; cannabidiol or CBD oil is a non-euphorigenic cannabis product being used and investigated for potential medicinal uses; high-potency synthetic cannabinoids, sometimes marketed as K2 or spice, are particularly toxic products psychiatrically

Potency: has more than doubled or tripled for typical smokable forms, with more refined, concentrated forms like hash oils even more potent; note that much research on long-term consequences on cognition began when potency was lower

Effects: acute intoxication results in impaired concentration, focus, problem solving ability, and memory; psychiatric complications can include anxiety, agitation, paranoia, and mood lability; with increasing potency of current products, including synthetic cannabinoids, there have been escalating reports of frankly psychotic symptoms and suicidality; data is mixed for longer-term impact on cognitive function, particularly for low-level use, but it is apparent in heavy regular users, particularly those that start use in early adolescence; onset of use before age 17, or particularly before 15, can have persistent and potentially profound impacts on central nervous system, affecting neuroconnectivity, frontal lobe development, and memory systems; normal CNS maturation, known to continue into early or mid-20s, can be affected in potentially profound and subtle ways; behavioral consequences of chronic use can include decreased motivation, decreased academic or job performance,

lower educational attainment, and reduced workplace productivity; consequences are variable, depending on amount of use and age at which use was initiated; physical dependence and withdrawal do exist and can complicate attempts to discontinue; pulmonary consequences are a concern, though few links have been established except in daily heavy smokers; risk may be mitigated through use of vaporizers or edible products; overdose has not been a concern with cannabis as an isolated agent; may change with increases in potency; evidence of impaired cognition and reaction time and divided attention support increased risk of accidents, as do some studies; evidence and opinion are divided; one concern is effects of increased availability and escalating potency on risks

Presentation: could include any of these issues, such as problems with cognition or memory, mood disorder, and/or personal and interpersonal problems, pulmonary symptoms, or accidents; with high potency products, could include acute psychosis, bizarre behavior, and suicidality; presentations in adolescence may range from subtle mood changes, including excitability or irritability, to depression, deterioration in school performance, change in appearance, change in peer group, decreased activity and isolating behavior, and change in financial status, worse or better; this set of symptoms can present for all substance use disorders in adolescence; this pattern can also relate to mood disorders independent of substance use; warrants a comprehensive mental health evaluation

Stimulants: next most commonly abused class; includes cocaine, methamphetamine, and ecstasy, as well as illicitly or inappropriately used preparations such as amphetamine and methylphenidate; can be taken orally, snorted, smoked, or injected; provide euphoria, energy, and alertness; potential side effects of agitation, fearfulness, paranoia, and sexual dysfunction;

Ecstasy or MDMA: considered a hallucinogen as well as a stimulant; use results in a feeling of increased closeness to others, empathy, and tactile sensitivity

Cocaine: most readily available in US in two forms; purified cocaine hydrochloride is traditional powdered form that can be snorted or injected, with effects that can last a short time to a few hours; crack cocaine is a base form that is marketed as small pebbles; heat stable and can be smoked; smoking allows quicker, more dramatic response similar to but faster than injecting or snorting powder; produces intense euphorigenic experience; wears off quickly, inducing craving to use and reuse; leads to a binge-crash cycle of abuse

Methamphetamine: powdered and smokable forms; effects and complications similar to cocaine, particularly crack cocaine; easily and cheaply synthesized from readily available ingredients; provides intense rapid onset from smoking or injecting; associated with social deterioration, aggression, and psychiatric complication

Medical complications of stimulant use: diverse, potentially catastrophic, and unpredictable; worst relate to cardiovascular and psychiatric complications; cardiovascular complications include coronary and cerebral artery spasm; may lead to anginal pain, myocardial infarction, stroke, or seizures; effects on pacemaker function can result in serious arrhythmias, including cardiac standstill and sudden death; potentially fatal complications independent of route of administration or form of drug; psychiatric complications can be mild to serious, ranging from dysphoria to depression to suicidal intent; agitated behaviors range from fearfulness to anxiety to paranoia, hypomania, and psychosis, particularly paranoid psychosis; increasingly supplemented with fentanyl and fentanyl analogs with increase in potency and overdose risk

Opioids: includes illicit drugs like heroin or fentanyl, as well as prescription opioid analgesics; great public and medical concern recently; availability and use of opioids and the associated problems have surged in the past 15 years with more liberal prescribing of opioid analgesics for pain; problem has escalated further with the availability of purer, cheaper heroin supplemented with fentanyl and even more potent fentanyl analogs; these prescription drugs are typically taken orally; can be snorted or injected; heroin can be snorted, injected, or smoked; most abused opioids are fast-onset, short-acting products; long-acting preparations are frequently manipulated to allow faster and more potent onset of action; all can be used for euphoria, particularly when snorted or injected; also used for pain relief, calming, or sedation; individuals may be energized and activated; some use these drugs for performance enhancement; the long-acting, slow-onset character of some opioids like methadone or the partial agonist buprenorphine give them the potential for use as therapeutic agents

Complications: these include overdose; also include injection-related soft tissue and cardiac infections, hepatitis B and C, infectious diseases related to lifestyle and environment, such as tuberculosis and STDs, and withdrawal symptoms; the opioid-dependent user may present with a range of medication-seeking behaviors; the distinction between misuse or addiction and inadequately treated pain may only become apparent when patient is seen over time; patterns of compliance or misuse can be noted and substance use and psychiatric comorbidities can be identified

Overdose: needs to be promptly recognized; patient presents as unconscious and poorly responsive; pinpoint pupils and slow, shallow respiration; prompt intervention with naloxone (Narcan) by rescue personnel, in the emergency room, or by peers can be lifesaving; prevention is best accomplished through access to addiction treatment and discontinuation of overuse behaviors

Role of Clinician

Overview: role varies depending on time, interest, and patient demographics; should be able to screen for and evaluate substance use problems even when not obvious; should be able to provide intervention appropriate to the level of problems, ranging from relatively brief interventions for those with mild or moderate risk or a referral for evaluation and treatment for those with severe substance use disorders; in more severe cases, there is the potential for prescribing adjunctive medications as well as providing supportive follow-up and reinforcement of interventions

Evaluation: relies primarily on self-report and report of family members or others to establish a working assumption of a patient's position on the continuum from use to addiction; can be supplemented by medical history

review looking for recurrent problems such as trauma or other situations associated with drug use; physical exam findings such as track marks or abnormal lab findings such as increased liver function tests may be suggestive; more often than not, physical exam and lab results will be noncontributory

Questioning about alcohol and drug use: should be asked routinely at health maintenance visits or whenever patient presents with problems associated with substance use; questions should be direct and nonjudgmental and establish a collaborative orientation; this can be facilitated by the use of an appropriate transition statement relating the questions to the patient's presenting concerns. An example from a health maintenance visit might be, "drug and alcohol use can have a significant impact on your health, so I'm going to ask a few questions about your use of alcohol and other drugs." For a complaint of depression could use, "one thing that can make depression worse is alcohol and drug use, so I need to ask some questions about that."

Screening: screening instruments or health questionnaires can be a helpful part of the routine review of systems; can use single-item screening questions such as "have you had problems in the last year with alcohol or drugs?"; the Alcohol Use Diagnostic Inventory Test or AUDIT is useful, well validated instrument consisting of ten questions that can be given in oral or written form; has been validated in multiple languages; asks about problems with alcohol as well as quantity and frequency questions; can help screen for high-risk as well as problematic use; self-report is important; the perspective of a spouse or other family member should be sought out when available

Terminology: "standard drink" refers to fact that beer, wine, distilled spirits, liquor, and most customary drinks contain about the same amount of alcohol per serving; 12 ounces of beer, five ounces of wine, or one-and-a-half ounces of liquor contain about the same amount of alcohol; allows the user to titrate to tolerance and preference across products; an important part of questioning about drinking; when asking how many drinks someone has, important to clarify what is meant by "standard drink;" patients may not know because they don't measure or keep track, but this is useful information as well; some craft beers have double or more the standard concentration of alcohol, nine or ten percent versus four or five percent; many fruit coolers and other designer drinks have higher concentrations

Tools for further evaluation: include urine toxicology screens, breathalyzer testing, labs such as liver function tests and mean corpuscular volume; can be useful to check the prescription monitoring program in your state to look for use of potentially abusable medication

Intervention and Treatment

Overview: questions and evaluation most often identify low- or moderate-risk behaviors; provide opportunities to reinforce low risk behaviors, provide brief interventions to encourage lower-risk patterns or to leave open the door for further discussion or referral; may take only a few minutes to educate about lower risk or warning signs

Recommendations: for men, average no more than 14 drinks per week and no more than four drinks per occasion; for women or those over 65, seven drinks per week and no more than three per occasion; no use in high-risk situations like driving or with certain medications; warning signs are to encourage patients to pay attention to internal sense of problems or concerned feedback of others; it has been shown that such brief interventions have significant impact; simply asking these questions, having individuals think about their use, results in some individuals decreasing the amount they drink or use over time

Evaluation and intervention: need to evaluate readiness or motivation to change; involves asking questions that gauge awareness and acceptance of problem drug use and readiness to change those behaviors, including dealing with ambivalence regarding taking the steps needed; helps clinician match the intervention to the person's particular readiness and motivation to change; one behavior change model posits that change requires that individuals must first recognize and connect their behavior to the problems it is causing and weigh the pros and cons of the change before deciding or planning for change, taking action, and then maintaining the new behavior; interventions must be in sync with individual's change stage or is likely to be disregarded; if patient is thinking about whether drug use is a problem, intervention is to promote information making the connection; if patient is contemplating change, intervention is to help the patient see benefits of change as it relates to his or her particular goals; if patient is ready to take action, clinician can help patient identify treatment and medication options; it is likely that most patients will be ambivalent about some or many steps; goal is to help the patient resolve ambivalence and move forward

Word choices: ambivalence may be apparent; phrases like, "I want to," "I need to," "I should," or, "I would if only," indicate patient is indecisive; a referral or prescription is unlikely to be used; interventions are more likely to be implemented when you hear phrases like, "I am ready," "I have decided," or, "I will," when discussing next steps

Treatment options: for moderate-to-severe substance use disorders, the addiction end of the spectrum, much emphasis is put on inpatient, medically managed options like traditional 28-day residential programs; needed when medical risks such as severe withdrawal, unstable medical conditions, or psychiatric conditions like suicidal ideation are present; generally, though, treatment options using outpatient counseling of greater or lesser intensity are appropriate; there are multiple alternatives; support and self-help groups such as Alcoholics Anonymous (AA), Narcotics Anonymous (NA), Smart Recovery, Women for Sobriety are useful, readily available, and inexpensive; psychosocial, non-pharmacologic treatments such as cognitive behavioral therapy, motivational enhancement therapy, contingency- or incentive-based therapy, and couple's therapy can be implemented either in one-to-one counseling or combinations of individual and group counseling

Withdrawal and management: important to assess patient for current or potential withdrawal; ask about prior withdrawal; observe for agitation, irritability, restlessness, tremors or shakes, nausea, sweating, feeling hot and cold or flushed, and increased heart rate; generalized nervous system excitability is present for most kinds of withdrawal; seeing or hearing things, disorientation or delirium, or seizures are mostly associated with alcohol or other sedatives, particularly short-acting sedatives; complaints of aching, cramping stomach, jerking or restless legs, diarrhea, runny nose, dilated pupils are characteristic of opioid withdrawal; paying attention to these distinctions,

along with doing a drug screen, can identify drug use not reported by patient; management requires supportive care and medication

Treatment recommendations for specific substances

Cannabis: typically manifests as dysphoria, agitation, irritability, or insomnia; generally treated with supportive care rather than medication; some reports of benefit from dronabinol or Marinol for acute withdrawal; evidence is equivocal; this is an off-label use

Cocaine and other stimulants: primarily requires supportive care to deal with the crash that follows binging; important to assess and manage suicide risk, which can be serious and may require a monitored setting

Nicotine: nicotine replacement products like patch, gum, and inhaler can be used to manage withdrawal along with anti-craving medications like bupropion and varenicline

Alcohol and other sedatives: considered to represent the greatest medical risk because of potential for associated seizures and delirium; if patient reports a history of these, it generally indicates the need for monitored withdrawal in an inpatient setting; however, most do not have that history and can be managed at home if there is adequate family support to monitor a benzodiazepine taper, typically of six to eight days

Benzodiazepines: usual standard is a long monitored tapering process, generally outpatient; long-acting agents are generally substituted for short-acting, such as clonazepam for alprazolam; tapers are done slowly, such as ten percent every two to four weeks with monitoring by family and close management of prescriptions with regular visits and no refills; often difficult to accomplish in outpatient setting because of ease and risk of relapse; should be realistically discussed with patient and family; more rapid inpatient, monitored alternative may be more realistic and potentially successful

Opioids: symptomatic treatment uses variety of non-opioid medications, such as non-steroidal anti-inflammatories, clonidine (oral or extended-release), sedatives, and anti-emetics; high risk of relapse; close monitoring is needed if attempted as an outpatient; other outpatient option is to substitute and taper methadone or buprenorphine; methadone requires licensed clinic or program; buprenorphine can be through any DEA-waivered clinician; important to stress to patient that treatment of withdrawal is only a start; refer for behavioral treatment, peer support, or medication-assisted treatment; otherwise relapse potential is very high

Medication-assisted treatment

Important but often underutilized; medications can be used for withdrawal management and to treat associated medical and psychiatric comorbidities; medications specific to addiction help with craving or relapse; can help increase time abstinent, which is critical to allow reset of neuroadaptation and to restore cortical function; diminish craving and improve effectiveness of behavioral interventions; can mitigate reward associated with slips and decrease chance of slips progressing; there are FDA-approved medications for treatment for alcohol, nicotine, and opioid-use disorders; none for cannabis, cocaine, or other stimulant use disorders

Alcohol: disulfiram (Antabuse) has been in use the longest; taken once a day or three times a week; interferes with alcohol metabolism, causing toxic reaction with minimal alcohol use; reaction varies; can range from dysphoria, nausea, lightheadedness, or headache to severe vomiting and prostration; outcome literature is equivocal; evidence of increased effectiveness in those who are clearly motivated to stop, or who are using medication with observed monitoring; naltrexone is an opioid antagonist that interferes with alcohol's rewarding effect; studies show that for many minimizes craving to use, increases days without use, and decreases amount used; primarily used to work toward or maintain abstinence; also used to decrease alcohol use to lower, less problematic levels; available as oral and intramuscular, sustained-release preparations; sustained-release preparation has a better outcome due to improved compliance, but can be limited by higher cost; third FDA-approved medication for alcohol use disorder is acamprosate; literature support is weaker; reported to decrease internal agitation associated with craving and to therefore decrease chance of relapse

Opioids: naltrexone is FDA approved for treatment of opioid use disorders; binds strongly to mu opioid receptors; blocks ability to gain rewarding effect; significant decreases in craving and in use; oral and sustained-release preparations available; use of the sustained-release limited for some by cost; patient ambivalence can limit acceptance; opioid agonist medications, sometimes known as substitution-dependency treatments, are currently medication mainstays for opioid use disorder treatment; methadone must be dispensed through a licensed opioid treatment program, so although methadone can be prescribed for pain, it cannot be used for addiction treatment in standard medical setting; buprenorphine is partial-agonist opiate authorized for medical office use; requires DEA license waiver, which requires brief training and registration; with both methadone and buprenorphine, cross-tolerance prevents opioid withdrawal, minimizes craving, and blocks the euphoric effects of other opioids; chronic pain is a common comorbidity with opioid addiction; methadone and buprenorphine are effective opioid analgesics

Buprenorphine: potential advantages over methadone; partial agonist; demonstrates ceiling effect below level of respiratory depression; minimizes overdose risk; slower onset and lower reinforcing effect than full agonists; high affinity for mu receptor; effective in blocking rewarding effects of other opioids; effective analgesic; fewer side effects and risks than the full agonist methadone; several preparations, which have become progressively less expensive; month-long, subcutaneous, sustained-release preparation available; clinician with DEA waiver can provide effective, time-saving treatment without need to refer out

Summary of opioid use disorder: detox alone is seldom treatment of choice; medication-assisted treatment has better long-term outcomes than non-medication-assisted treatment; buprenorphine and naltrexone have some significant advantages in safety profile and availability in standard medical care settings; methadone may be useful for those that need added structure of treatment center

Chronic disorder management model: substance use disorders, particularly when severe, are best considered and treated as chronic diseases; require ongoing process of outcome evaluation with monitoring and adaption of treatment over time, with goal of long term management

rather than an all-or-none cure; can have variable course of active disease and remission; if there are relapses, individual should be reevaluated in terms of motivation and treatment involvement; may be adequate to recognize slip as normative and reinforce a return to previous supports; other times, evaluation will indicate need to treat or refer for psychiatric comorbidities; if not previously used, medication-assisted treatment should be reconsidered

Suggested Reading

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Hepatobiliary System

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Liver Diseases

Liver function tests (LFTs): albumin, test for synthetic function; direct bilirubin reflects conjugated bilirubin; elevation suggests hepatocyte dysfunction or cholestasis; indirect bilirubin, reflects unconjugated bilirubin, elevation due to extrahepatic etiologies, such as red blood cell hemolysis; alkaline phosphatase (ALP), produced by hepatocytes on their canalicular membranes, elevation reflects status of biliary system; elevation also seen in bone disease, eg, Paget's; ALP also produced from intestinal tract, placenta; elevation of ALP during pregnancy normal, all other elevated components abnormal in pregnancy, require further investigation; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), more specific for hepatocyte injury; AST in hepatocyte mitochondria and also in skeletal muscle; elevations in rhabdomyolysis and muscle injury such as trauma, typically disproportionate AST/ALT ratio; gamma-glutamyl transferase (GGT) primarily produced in biliary epithelium, more specific than ALP

Patterns of LFT abnormalities with specific liver diseases:

Acute viral hepatitis: high AST, ALT denotes hepatocellular involvement; also ALP and bilirubin elevations, not quite as high as AST, ALT

Alcoholic liver injury: tends to have 2:1 AST/ALT ratio

Non-alcoholic steatohepatitis (NASH): ALT higher than AST but not always

Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), ductal obstruction: cholestatic pattern, ALP and bilirubin elevation

Wilson's disease, Wilsonian crisis: elevated AST, ALT, but ALP disproportionally low; Wilsonian crisis also elevated indirect bilirubin, due to Coombs-negative hemolysis

Ischemic liver injury: high AST, ALT, then dip due to improvement, followed by slow rise of bilirubin

Diagnosis: liver function; albumin, bilirubin, prothrombin time and international normalized ratio (PT/INR) also reflect liver condition; note timeframe for injury, how long patient has had LFT abnormalities; travel history, potential viral cause; medication, new antibiotic, acetaminophen user; intravenous drug use, infectious disease; clinical history, diabetes, high blood pressure, hyperlipidemia, potential metabolic cause for LFT abnormalities

Viral hepatitis: hepatitis A, B, C, D, and E; herpes simplex virus (HSV); cytomegalovirus (CMV), Epstein-Barr virus (EBV); hemorrhagic virus, eg, Lassa fever, Ebola

Hepatitis A: self-limited, no chronic infection, incubation period 28 days, transmission fecal-oral route; tends to occur in outbreaks related to foods, especially fresh fruits and vegetables; in 1% of cases/year fulminant liver failure, especially if patient has underlying chronic liver disease; risk to acquire hepatitis A travel to endemic countries, food intake, men who have sex with men, household or daycare; in these cases consider immunoglobulin to prevent recurrence

Symptoms and diagnosis: nonspecific; fatigue, malaise, fever, nausea, vomiting, abdominal pain, jaundice; LFT pattern hepatocellular or mixed with bilirubin <10 mg/dL; AST, ALT high, into thousands; order IgG and IgM; IgM elevated in acute infection, IgG in previous infection or vaccination

Treatment: prevent with vaccination; in acute setting supportive care, post-exposure prophylaxis of household contacts, particularly immunosuppressed, sexual partners, child daycare centers, food handlers; prophylaxis within 2 weeks of exposure via infusion of immunoglobulin; guidelines recommend immunoglobulin to people >41 years and children <1 year, also contacts with baseline chronic liver disease, immunocompromised

Hepatitis B: DNA virus; ability to integrate into host hepatocyte genome; challenging to cure when chronic; treatment focused on viral suppression; chronic viral hepatitis B confers elevated risk for hepatocellular carcinoma (HCC), which can also occur without cirrhosis; most common cause of acute liver failure in world; transmission through blood contact like sharing needles, sexually, vertical transmission from mother to child common in some parts of world; incubation period weeks to 4-6 months, important for history and contacts

Symptoms and diagnosis: similar to hepatitis A; malaise, jaundice, abdominal pain, fever, nausea, vomiting; diagnosis by serology; surface antibody, core antibody, surface antigen, envelope (E) antigen, DNA of virus; IgG (prior infection or vaccination) and IgM (acute infection) of surface and core antibodies; presence of hepatitis B antigen denotes active or chronic infection or immunotolerant state; liver biopsy not essential for diagnosis, used to assess degree of inflammation, presence of fibrosis or cirrhosis; treatment depends on serologic markers, DNA level, transaminases; cutoffs for DNA levels, ALT levels and presence of E antigen, cutoffs help decide when to start treatment; not always necessary to treat chronic hepatitis B

Treatment: no cure yet; suppression of viral replication with antivirals improves inflammation status,

decreases progression to cirrhosis and HCC; common antivirals tenofovir and entecavir; tenofovir can be used in pregnancy; other antivirals lamivudine and telbivudine, both have higher potential to develop and drive hepatitis B resistance; peginterferon in certain genotypes for hepatitis B, check for genotypes only in specialty practice; vaccination is the best prevention of complications; babies vaccinated before leaving hospital; to minimize vertical transmission, newborns get vaccine and hepatitis B immunoglobulin (HBIG), reduces risk significantly; antivirals used in third trimester when viral levels >200,000 IU/mL

Screening: hepatitis B can cause HCC without presence of cirrhosis; patients with chronic hepatitis B and cirrhosis should have HCC screening every 6 months, ultrasound with or without α-fetoprotein; screening in patients with chronic hepatitis B with or without cirrhosis every 6 months with family history of HCC; Asian men with chronic hepatitis B >40 years old and women >50 years; patients from sub-Saharan Africa >20 years old should be screened, as viral hepatitis B acquired in Africa is more aggressive, more oncogenic phenotype

Hepatitis C: RNA virus; chronic infection can lead to cirrhosis; CDC recommends serology screening for hepatitis C in individuals born between 1945 and 1965; 15% to 20% of patients who acquire hepatitis C spontaneously clear virus; the rest develop chronicity, which can lead to cirrhosis; liver failure can occur with acute hepatitis C in patients with underlying chronic liver disease (alcohol cirrhosis, cirrhosis secondary to chronic viral hepatitis B); risk for hepatitis C acquisition is intravenous drug use, needle sharing, blood transfusion before 1990 (no regularly screening for hepatitis C until then), sex (efficiency of virus transmission generally low), safe sex practices important for patients with chronic viral hepatitis C

Symptoms and diagnosis: nonspecific; jaundice, abdominal pain, malaise, nausea, vomiting; onset of symptoms 7 weeks to 6 months after infection; many patients asymptomatic; diagnosis by hepatitis C antibody with PCR to confirm active viremia; in acute setting antibody level often negative; check PCR if clinical situation of patient suggests hepatitis C; if serology positive, but PCR negative, patient has spontaneously cleared virus

Treatment: after active viremia confirmed, determine genotype to delineate what type of hepatitis C virus; determines type of treatment; hepatitis C used to be treated with interferon and ribavirin, long treatments, rough side effects, clearance rates low; today hepatitis C can be cured with sustained virologic responses of 95% to 97%, regardless of genotype, presence of cirrhosis, or if patient was treated before; today treatment is moving target, newer pan-genotypic agents, treatment simplified and shorter; in past treatment course was 12 to 24 weeks, with newer drugs can be as low as 8 weeks; interferon not used anymore, occasionally ribavirin used in combination with direct-acting antivirals, typically in specialty setting

Hepatitis D: also known as viral hepatitis delta agent; requires presence of hepatitis B for viral assembly; acquired by coinfection or superinfection; superinfection is new hepatitis D infection on top of baseline chronic hepatitis B

Treatment: prevent acquisition of hepatitis B; if hepatitis D is acquired, treatment is with interferon for months

Hepatitis E: RNA virus; fecal-oral route; zoonotic infection; food intake; often swine implicated in disease outbreak; risk factor is travel to endemic regions like Central America, Asia, Africa; conditions with more significant disease course include pregnancy, solid organ transplant patients, other immunocompromised patients; can get chronic infection; patients with pre-existing chronic liver disease are at elevated risk for significant injury from hepatitis E infection

Symptoms and diagnosis: similar to other viral hepatitides or asymptomatic; antibody testing; RNA PCR also available

Treatment: supportive in acute setting; in patients with immunosuppression and chronic infection, like liver transplant recipients, immunosuppressive medications are reduced and treatment is with ribavirin

Herpes simplex virus hepatitis: in immunocompromised or elderly; anicteric liver failure with high levels of AST/ALT but relatively low bilirubin; <50% of patients have herpetic dermatologic lesions; they have generalized systemic illness; pregnant patients have more significant disease course; have clinical suspicion and treat with antivirals like acyclovir

Cytomegalovirus hepatitis: immunocompromised population; self-limiting; biopsy histology shows classic owl's eye inclusions

Epstein-Barr virus: treatment supportive; antivirals rarely needed

Immune-mediated Diseases

Autoimmune hepatitis (AIH): female predominance; liver injury varies from LFT abnormalities to fibrosis, cirrhosis, need for liver transplantation, or acute liver failure; drugs like minocycline, nitrofurantoin can induce AIH; also checkpoint inhibitors, a newer class of cancer drugs that includes nivolumab, used for hepatocellular carcinoma

Symptoms and diagnosis: spectrum from asymptomatic to acute liver failure; hepatocellular pattern to LFT abnormalities; elevated antinuclear antibody, elevated anti-smooth muscle antibody, both >1:40; elevated IgG; there is also a subtype of AIH that is serology negative; liver biopsy to confirm diagnosis, look for interface hepatitis, a lymphocytic plasma cell-predominant inflammation

Treatment: immunosuppressants; prednisone; add azathioprine for steroid-sparing therapy; second-line drugs are budesonide, mycophenolate mofetil, tacrolimus; may be cirrhosis after AIH; recurrence after transplant possible in 20% to 30%; these patients left on low-dose prednisone

Overlap syndrome: elements of AIH, primary biliary cholangitis, or primary sclerosing cholangitis; liver biopsy drives treatment; treat what biopsy shows predominantly

Primary biliary cholangitis (PBC): formerly primary biliary cirrhosis, but not every patient develops cirrhosis; cholestatic disease; often middle-aged females

Symptoms and diagnosis: asymptomatic or LFT abnormalities to fatigue, dry eyes, dry mouth, pruritus; may develop cirrhosis; may develop portal hypertension

without cirrhosis; biopsy not necessary; diagnosis based on laboratory results — elevated ALP (1-1.5 times upper limit of normal); anti-mitochondrial antibody elevated in 95% with titer >1:40; liver biopsy (if done) shows non-suppurative cholangitis, granulomas; classic pathognomonic finding "florid duct lesion"

Treatment: ursodiol; second-line therapy obeticholic acid; be alert for associated disease with PBC; osteoporosis due to malabsorption of vitamin D; because bile acid lacking, there is also malabsorption of vitamin A, E, and K; in newly diagnosed patient, check for osteoporosis with vitamin D, calcium level, DEXA scan; replete vitamin D and calcium; pruritus common in PBC, besides ursodiol, treat with cholestyramine, rifampin, naltrexone, sertraline; hyperlipidemia seen in PBC, not associated with elevated risk of cardiovascular disease; xanthomas in patients with significant PBC

Primary sclerosing cholangitis (PSC): mostly young men; association with inflammatory bowel disease (IBD, both Crohn's disease and ulcerative colitis); 30% of those with PSC don't have IBD; elevated risk of cholangiocarcinoma; annual screening advised

Symptoms and diagnosis: jaundice, pruritus, fatigue; IBD symptoms; cholangitis in PSC patients with narrowed ductal anatomy; elevations in ALP and bilirubin typical; may have AST/ALT abnormalities; MRCP (magnetic resonance cholangio-pancreatogrphy) shows "beads on string" appearance due to segmental fibrotic areas in ducts; LFT and imaging findings enough to diagnose PSC; sometimes liver biopsy can be helpful to diagnose small-duct PSC (subtype of PSC); classic histologic finding is onion skin fibrosis around bile ducts, but this is very uncommon; typically see ductal inflammation, ductal proliferation, periductal fibrosis; avoid ERCP (endoscopic retrograde cholangio-pancreatogrphy) at all costs; dye and contrast in biliary system with fibrotic strictures difficult to drain, increases risk for colonization, cholangitis; manipulate biliary system only if absolutely necessary, eg, for cholangitis

Treatment: no treatment; cholangitis should be treated as it would be in patient with a stone; liver transplant has excellent outcomes; recurrence after transplant possible; occasionally second transplant necessary

Metabolic and Genetic Causes for Liver Disease

Hemochromatosis: common genetic cause of liver disease, multiple subtypes, majority autosomal recessive; accumulation of iron in liver; also heart, pancreas, bone joints

Diagnosis: abnormal LFTs; elevated transferrin, ferritin, total iron-binding capacity (TIBC); genetic testing; liver biopsy in patients >40 years and ferritin >1,000; degree of fibrosis and presence of cirrhosis

Treatment: phlebotomy; if disease caught early, phlebotomy can result in normalized life expectancy; chelation therapy also possible

Wilson disease: mutation in copper transporter within biliary system leads to increased copper levels; autosomal recessive; rare disease; patients <40 years; pediatric population; neurocognitive issues due to accumulation of copper in central nervous system; behavioral issues early sign in children, often overlooked

Symptoms: range from LFT abnormalities up to acute fulminant failure (Wilsonian crisis); requires liver transplantation for patient survival; LFTs in Wilson disease elevated AST, ALT and low normal ALP; low ceruloplasmin; 24-hour urine copper test helpful; slit lamp testing for Kayser-Fleischer rings; presence not necessarily pathognomonic for Wilson disease; liver biopsy for copper content

Treatment: chelation therapy with penicillamine, trientine; trientine first choice due to significant side effects of penicillamine; low copper diet

Alpha-1 antitrypsin (AAT) deficiency: autosomal recessive; can cause liver issues; mutation in serine protease that inhibits neutrophil elastase in lungs; genetic substitutions lead to protein misfolding; protein accumulates in hepatocytes due to lack of proper export; build-up results in liver damage, cirrhosis over time

Diagnosis: AAT level in blood; genotype and phenotype tests for type of disease; liver biopsy shows PAS-positive, diastase-resistant granules

Nonalcoholic fatty liver disease (NAFLD): increasingly common; 83 million individuals in US believed to have NAFLD; nonalcoholic steatohepatitis (NASH) stems from NAFLD; multifactorial, genetics, multiple comorbidities (eg, hypertension, diabetes, hyperlipidemia, obesity); increase of transplantations for cirrhosis caused by NASH

Diagnosis: LFTs mild transaminase elevations, ALT higher than AST; exclusion of other causes of liver injury; ultrasound shows change in echogenicity of liver; liver biopsy gold standard, though NASH can be diagnosed without; biopsy shows steatosis, hepatocyte swelling, ballooning, Mallory-Weiss bodies; shows degree of fibrosis, helpful for prognosis; elastography can test for fibrosis, tends to overdiagnose; MR (magnetic resonance) elastography more sensitive, specific; serology markers; scoring systems, currently undergoing reproducibility for fibrosis determination, may replace liver biopsy

Treatment: mitigating risk factors — weight loss, including bariatric surgery; improvement of diabetes control, reducing high cholesterol, high blood pressure; 7% to 10% reduction of body weight improves liver pathology; possible to reverse inflammation, steatosis, even fibrosis; newer treatments in clinical trials; drug therapy with vitamin E and pioglitazone have shown some promise

Drug-induced liver injury; most common cause of acute liver failure in US; two types; direct injury, dose-dependent, eg, acetaminophen; idiosyncratic drug injury, eg, antibiotics, herbal supplements; not all drugs cause acute liver failure, different degrees of injury; hepatocellular pattern in statin drugs; cholestatic pattern in antibiotics; autoimmune phenotype; fatty liver; fibrosis; leading cause of FDA regulations; onset is days to months after drug use; after 6 months of drug use, injury unlikely due to drug

Diagnosis: timing of drug exposure; rule out viral, genetic; LFT pattern; imaging; biopsy helpful, but role uncertain; may challenge patient with same drug to see if drug is actual cause of injury

Treatment: stop drug; N-acetylcysteine may help in idiosyncratic injury; definitely helps in injury due to acetaminophen; improves mortality, increases transplant-free survival; closely monitor patient; supportive care; early referral to liver transplant center in case of severe disease

Alcoholic liver disease: 75,000 patients/year and third leading cause of death in US; alcohol cirrhosis causes 35,000 deaths/year; second most common cause of liver transplant after hepatitis C; alcohol consumption worsens underlying liver disease like hepatitis C or B, increased risk for cirrhosis; degree of disease depends on amount of alcohol consumption; can cause steatosis, cirrhosis, or severe alcoholic hepatitis; alcoholic hepatitis is clinical diagnosis; laboratory values used to calculate discriminant function; discriminant function >32 suggests use of steroid therapy; STOPAH trial showed steroids not as helpful as once thought, especially in long term; in guidelines, use of steroids in right clinical scenario; risk factors are alcohol intake and amount, not type of alcohol; genetics plays important role, as do ethnicity, history of bariatric surgery, obesity, gender

Diagnosis: history; laboratory results, 2:1 AST/ALT ratio, but not always present

Treatment: complete abstinence from alcohol; significant complications from long term liver disease

MELD score = model for end-stage liver disease; scoring system to determine severity, predict 90-day mortality; equation based on laboratory factors, bilirubin, creatinine, INR, sodium; used to prioritize wait list for liver transplantation; higher score, higher mortality risk; maximum score 40 points; MELD system replaces Childs-Pugh score

Complications of Chronic Liver Disease

Portal hypertension: combination of static, dynamic changes within liver vasculature; alterations in portal flow characteristics, increased portal vein pressures; can cause esophageal varices, gastric varices, ectopic varices; engorged veins due to elevated portal pressure

Variceal bleeding: life-threatening; all patients with cirrhosis should be screened with EGD (endoscopic gastroduodenoscopy)

Treatment: if high risk of bleeding, can band esophageal varices with rubber bands placed on varices; multiple sessions, varices scar down, risk for de-bleeding reduced; non-selective beta blockers, nadolol or propranolol, also treatment options; bleeding varices — hemodynamic stabilization with IV fluids, blood products; ICU; octreotide, causes splanchnic vasoconstriction; antibiotics most important, improves mortality and re-bleeding rates; emergent upper endoscopy within 12 hours of admission to band bleeding varix if possible; transjugular intrahepatic portosystemic shunt (TIPS) if bleeding uncontrolled; generally considered salvage therapy, but has been used as early bleeding therapy

Ascites: most frequent complication of portal hypertension; accumulation of fluid in peritoneal space

Diagnosis: physical exam, ultrasound; paracentesis should be done in every cirrhotic patient with ascites; labs to do on peritoneal fluid — total albumin, total protein, white blood cell count with differential, cultures both aerobic and anaerobic; calculation of serum-ascites albumin gradient (SAAG), subtract ascites albumin from serum albumin; if SAAG >1.1, ascites accumulation indicative of portal hypertensive source; ascites can also accumulate as result of heart failure, total protein helpful to determine if ascites from portal hypertension or heart failure; total protein >2.5 possible echocardiogram

Treatment: diuretics, spironolactone and furosemide; low sodium diet, <2 g; if diuretic resistance, TIPS; if MELD >20, TIPS contraindicated, can induce further liver failure; due to infection risk, avoid permanent percutaneous catheter; only use in palliative care

Spontaneous bacterial peritonitis (SBP): risk in ascites; should be high in differential in cirrhotic patient with acute onset of hepatic encephalopathy, fever, abdominal pain, unexplained leukocytosis

Diagnosis: total neutrophil count in ascetic fluid >250 and/or positive culture

Treatment: antibiotics, albumin to lessen risk of acute kidney injury as result of infection; secondary prophylaxis with use of chronic antibiotics after resolution of acute episode

Hepatic encephalopathy (HE): hepatic dysfunction in shunting, causes impairment in neurotransmission within central nervous system; ammonia neurotoxin, comes from enterocytes and colonic bacteria within GI tract

Diagnosis: clinical diagnosis; measurement of ammonia, can be low or high; symptoms range from minimal HE, which requires specific psychometric testing to diagnose, to coma; must investigate cause; potential causes for HE are infection, GI bleeding, non-compliance with lactulose, medications like benzodiazepines, opioids,,dehydration from lack of fluid intake, fluid diuresis, diarrhea or too much lactulose

Treatment: treat actual cause of HE; use lactulose, which acidifies GI tract lumen, turns ammonia into ammonium, easier to pass; rifaximin, helps control bacterial load that contributes to ammonia levels; in resistant HE investigate for shunts with cross-sectional imaging with MRI or CT scan; do not restrict protein intake in patients with cirrhosis to minimize HE; patients are typically nutritionally deficient and in catabolic state; restriction of protein harmful to overall nutritional status, makes no difference for HE

Hepatopulmonary syndrome: systemic complication of HE; decreased liver clearance of vasodilatory compounds that come from the gut due to cirrhosis; results in pulmonary vascular dilatation, decreased arterial blood oxygenation; patients experience hypoxia, low PaO_2 (partial pressure of arterial oxygen); platypnea — patient is short of breath sitting up; dyspnea relieved by lying down

Diagnosis: echocardiogram with microbubbles; during echo, microbubbles injected intravenously; if bubbles pass from right side of heart to left side of heart within 3 to 6 cardiac cycles, diagnostic of hepatopulmonary syndrome

Treatment: supplemental 0_2, liver transplantation

Portopulmonary hypertension: stems from cirrhosis; pulmonary arterial (PA) pressure elevated; PA pressure >35 mm Hg contraindication to transplant

Diagnosis: echocardiogram; cardiac catheterization to measure PA pressure

Treatment: pulmonary vascular dilators, sildenafil; in candidates for transplantation, portopulmonary hypertension confers MELD exception points; prior to transplantation PA pressure must be <35 mm Hg, reached with pulmonary vascular dilators or not

Immunizations: vaccinate patients with cirrhosis against hepatitis A, B; potential transplant candidates should have live vaccines, including MMR (measles-mumps-rubella) and shingles; after transplantation patients immunosuppressed, cannot get live vaccines

Nutrition: optimization of nutrition prior to transplantation; should have 35 to 40 kcal/kg/d; protein 1.2 to 1.5 g/kg/d; bedtime snack helpful

Osteoporosis: potential complication; screening indicated for all cirrhotic patients; obtain vitamin D, calcium level; regular DEXA scans; esophageal varices are not contraindication for bisphosphonate use; medications in cirrhosis adjusted for hepatic impairment

Drug-induced liver injury: patients with cirrhosis not at increased risk, but if it does occur, symptoms will be more severe if cirrhosis present; cirrhosis patients should completely avoid NSAIDs; for pain Tylenol <2 g/day can be given; NSAIDs cause afferent arterial vasoconstriction in kidney, worsening kidney injury can have significant impact on cirrhotics; avoidance of herbals; not regulated by FDA; numerous case reports of herbals causing acute liver failure; avoidance of alcohol

Acute liver failure: defined as onset of coagulopathy with INR >1.5 followed by encephalopathy within 8 weeks in patient without prior history of liver disease; dramatic, occurs rapidly, extremely sick patients; ICU, intubation, sedation; cerebral edema can occur due to high levels of ammonia; most common cause in US is drug-induced, in world hepatitis B; also hepatitis A, Budd-Chiari, amanitin mushroom toxicity, Wilson's disease, pregnancy, AIH; 30% to 40% of cases of acute liver failure spontaneously resolve with ICU care and do not require liver transplantation

Liver transplantation: acute liver failure has preferred listing status with UNOS (United Network for Organ Sharing), status 1A; refer patient promptly to transplant center; common causes for liver transplantation hepatitis C, alcoholic liver disease, NASH; MELD score for waiting list; patient's blood type; location of transplant center; overall 1-year survival rate for liver transplant patients 85% to 90%; depends on etiology of liver disease — cholestatic etiologies do better than acute liver failure, only at about 80%

Liver Lesions

Hepatocellular carcinoma (HCC): third most common cause of cancer-related death in world; cirrhosis from any cause is risk factor for HCC; screening of cirrhotics every 6 months with ultrasound, with or without α-fetoprotein (AFP); elevated AFP and normal ultrasound should prompt additional imaging for smaller HCC with 3 phase CT scan or MRI

Diagnosis: imaging alone; biopsy not necessary; specific findings on cross-sectional imaging, arterial enhancement with delayed venous washout in pseudocapsule; elements of lesion fed into scoring system LI-RADS (liver imaging reporting and data system); LI-RADS score of 5 diagnostic for HCC

Treatment: depends on size, location, level of cirrhosis, portal hypertension, reserve of liver; resection if no portal hypertension, good synthetic function, location surgically amendable; transplantation, local regional treatments by interventional radiologists can bridge patients to transplantation; systemic treatments, sorafenib and newer second line agents if patient not a candidate for resection or transplantation

Cysts: benign; no clinical significance; found incidentally

Cyst adenomas: potential to develop cancer; evidence of mural nodule, wall irregularity on ultrasound; should prompt additional imaging modalities; biopsy

Focal nodular hyperplasia (FNH): benign; more women than men; found incidentally; typical central scar; management supportive; no need to hold oral contraceptives

Adenomas: malignant potential; associated with oral contraceptive use; stop use to minimize growth; if >5 cm surgery to remove; <5 cm monitor with regular imaging; in men, removal of adenoma regardless of size

Hemangiomas: benign collection of blood vessels, very common; surgery only if large or patient is symptomatic

Liver abscesses: managed with antibiotics, percutaneous drainage; often enteric source such as *E. coli* or other anaerobic bacteria

Vascular Disorders

Budd-Chiari syndrome: thrombosis within hepatic vasculature; risk factors anything that causes hypercoagulable state, such as polycythemia vera, factor V Leiden; workup should be done for cause; secondary causes are tumor and IVC (inferior vena cava) webs

Diagnosis: ultrasound Doppler; cross-sectional imaging; may be complications like portal hypertension or liver failure; cirrhosis can result from chronic outflow obstruction

Treatment: anticoagulation; TIPS; liver transplantation

Portal Vein Thrombosis: in cirrhotics portal flow velocities reduced; causes blood stasis within portal vein, clot formation; collateral blood flow development, cavernous transformation; anticoagulation in setting of cirrhosis controversial

Acute portal vein thrombosis: can result in portal hypertension, abdominal pain, fever, ascites; extension into mesenteric vein can occur, impacting intestine, causing congestion, ischemia

Treatment: anticoagulation; thrombolytic therapy by intravenous catheters

Biliary System

Components: gallbladder and biliary tree; primary highway for bile; bile acts as surfactant, hydrophobic and hydrophilic components, aids in fat emulsification, can neutralize acid, bactericidal elements in GI tract; biliary tree collects and drains bile that is produced in liver and drains into duodenum; gallbladder allows for bile storage, used whenever needed for significant fat load from meal; common bile duct should be <6 mm, dilatation with choledocholithiasis; intrahepatic ducts start in liver, drain into common hepatic duct, common bile duct, which extends into duodenum, where sphincter of Oddi muscle regulates flow of bile into duodenum, gallbladder connected via cystic duct

Gallstones: stones can get stuck in cystic duct or sphincter of Oddi; cholesterol stones, most common; brown stones result from chronic biliary tract infection with enteric bacteria, parasites; black stones seen in cirrhosis, patients with chronic hemolysis, like sickle cell disease; risk factors for cholesterol stones high serum cholesterol, obesity, diabetes, terminal ileal disease

with bile acid malabsorption, pregnancy; in pregnancy, stasis in gallbladder due to increased progesterone and increased cholesterol formation due to increased estrogen; progesterone also decreases bile acid secretion; slight variances between ethnicities; 70% of patients with stones asymptomatic and no treatment is indicated

Acute cholecystitis: stones obstruct cystic duct, lead to gallbladder wall inflammation due to bacterial factors, components in bile

Choledocholithiasis: stones obstruct common bile duct; leading cause of symptomatic obstructive jaundice; if stone lodged in biliary tree, can cause increased biliary pressure, enteric bacteria (*E. coli*, *Klebsiella*, *Pseudomonas*) translocate from GI lumen into bile duct

Diagnosis of cause of biliary colic: CBC, complete metabolic panel (CMP); ultrasound in fasting state to minimize bowel gas; has high sensitivity and specificity; assessment of gallbladder size, wall thickness, internal components, biliary tree, cystic duct, diameter of common bile duct; CT scan, MRCP, also very sensitive/specific; less invasive than ERCP or endoscopic ultrasound; HIDA scan, high sensitivity and specificity, but not helpful in chronic liver disease

Treatment: if symptomatic, intravenous antibiotics and fluids, then laparoscopic cholecystectomy

Acalculous cholecystitis: gallbladder inflammation, not obstructive process; very sick, ICU; risk factors elderly, chronic systemic illnesses like HIV, vascular diseases; fever of unclear origin, sepsis due to perforation of gallbladder

Treatment: supportive, antibiotics; percutaneous cystostomy tube until cholecystectomy possible

Cholangitis: complication of choledocholithiasis; Charcot's triad with jaundice, fever, right upper quadrant abdominal pain; life-threatening

Treatment: antibiotics; ERCP with stone removal

Gallbladder cancer: risk factors include stones due to chronic inflammation, obesity, polyps, PSC, congenital biliary cyst; no specific clinical features, late diagnosis; 5-year survival rate 5%

Treatment: surgery; adjuvant therapy not established; trials include radiotherapy; palliative chemotherapy

Cholangiocarcinoma: late diagnosis; jaundice, due to obstruction of biliary system; 5-year survival rate 10%

Treatment: surgery, generally for extrahepatic tumors; transplantation considered if tumor <2 cm in size, unresectable; chemotherapy, adjuvant and neoadjuvant approach

Suggested Reading

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Disorders of the Esophagus, Stomach, and Duodenum

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Overview: review of disorders of the esophagus, stomach, and duodenum; covering common clinical scenarios

Dysphagia

Diagnosis: location of the dysphagia, distally, in the chest, or proximally, in the neck; occurs with solids, liquids, or both; duration and progression of symptoms; if location is at neck, highly suggestive of oropharyngeal cause or disease within the proximal esophagus; possibilities include esophageal web, Zenker's diverticulum, cricopharyngeal hypertension, or cervical osteophyte in older patient; if patient coughing with drinking liquids, may be motility disorder involving the muscles of swallowing; can occur after stroke or in aging

Testing: modified barium swallow with assistance of speech therapist, information on abnormalities of process of swallowing, demonstration of cervical osteophyte impinging on the esophagus or Zenker's diverticulum; if muscles associated with swallowing involved, speech therapist can recommend management directly with patient; neck area not well visualized by endoscopy, which is used as second-line test for unclear diagnosis or to suggest therapy guided by previously obtained barium studies; if location of symptoms is at chest, disorder is esophageal dysphagia; endoscopy is first-line test; if dysphagia occurs with solid foods only, may be mechanical obstruction; if dysphagia occurs with liquids and solids, consider motility disorder or severe mechanical obstruction

Solid food dysphasia: to determine cause of dysphasia, timing very helpful; non-progressive dysphagia over years suggests benign mechanical causes, *eg,* Schatzki's rings

Schatzki's Rings: benign, mucosal rings that occur close to the gastroesophageal junction; treatment endoscopic

Eosinophilic esophagitis: patients with intermittent dysphagia starting in childhood or early adulthood, also history of allergies and atopy; benign, results from food allergens; diagnosed endoscopically; narrowed esophagus with ringed appearance; biopsies reveal many eosinophils, both distally and proximally; common allergens are milk, egg, soy, wheat, peanuts, tree nuts, fish, and shellfish; patients may have intermittent food impaction; food stuck in esophagus, patient unable to pass food bolus, sometimes unable to swallow secretions, often spitting up; centrally located chest pain not responding to antacids; upper abdominal discomfort; gastroesophageal reflux disease (GERD)-like symptoms and refractory heartburn not responding to typical antacids or proton-pump inhibitors (PPIs)

Treatment: high-dose acid suppression to decrease eosinophil counts and improve symptoms; Six Food Elimination Diet, stepwise elimination of allergens to improve symptoms, first milk, then egg, soy, wheat, peanuts, tree nuts, fish, and shellfish; if above ineffective, try topical corticosteroids (budesonide slurry or swallowed fluticasone); gentle repeated dilations may work in patients with not-very-active inflammation, more fibrotic changes within the esophagus, not responding well to steroids

Other conditions: possible causes of pain with dysphagia (odynophagia) are candida infections, viral diseases, severe reflux disease, pill esophagitis

Pill esophagitis: esophagus has several narrow points, pills can get stuck and cause local inflammation; most common site is proximal esophagus at transition of skeletal and smooth muscle, area of relative muscle weakness and anatomic area where aortic arch crosses and may press on esophagus; combination can result in material/pills getting stuck; commonly associated with antibiotics, such as tetracycline and clindamycin, bisphosphonates, potassium chloride, iron-containing compounds, non-steroidal anti-inflammatory drugs (NSAIDs)

Candida infection: consider in patients receiving steroids; mild to severe infection in the esophagus; if oral candida infection is diagnosed as well as dysphagia and odynophagia, treatment with antifungal prior to upper endoscopy

Viral disease: consideration of viral disease, such as herpes, in immunocompromised patients with dysphasia and odynophagia; diagnosed endoscopically with biopsy (histopathology, special staining)

Esophageal cancer: progressive dysphagia in older patients; history of heavy smoking, increased body mass, longstanding gastroesophageal reflux disease, and diet low in fruits and vegetables account for almost 80% of esophageal adenocarcinoma in US; diagnosed by upper endoscopy prior to any other diagnostic testing, especially in the presence of weight loss or risk factors

Motility disorders: conditions that affect the esophagus include achalasia, esophageal spasm, scleroderma, dermatomyositis, as well as nonspecific motility disorders uncovered by high-resolution manometry; first-line test is endoscopy to eliminate mechanical cause of dysphagia; next is high-resolution esophageal motility study; motility catheter is inserted into nostril and passed through gastroesophageal junction to measure peristalsis and pressure; routine high-resolution manometry (HRM) helps further characterize and improve management of diseases

such as achalasia, whether by endoscopic or surgical myotomy of the lower esophageal sphincter and distal esophagus

Achalasia: relatively uncommon; tightness of the lower esophageal sphincter, fails to relax normally with swallowing, loss of peristalsis in the body of the esophagus; symptoms of dysphagia, heartburn, and regurgitation; 3 different subtypes of achalasia can be diagnosed with HRM, but not discussed in lecture

Treatment: goal is relaxation of lower esophageal sphincter; in poor surgical candidates, Botox injection into sphincter can provide relief, tachyphylaxis does develop, and effect diminishes over time; surgery, if feasible, is preferred to disrupt sphincter mechanically, either with dilating balloons that can be expanded from 3 to 5 cm, or more commonly with surgical or endoscopic cutting of the circular muscle of the distal esophagus and lower esophageal sphincter

Gastroesophageal reflux disease (GERD)

Overview: estimated prevalence in the West 10% to 20% of population; symptoms include heartburn, regurgitation, chest pain, upper abdominal pain, nonproductive cough, and hoarseness

Physiologic factors: to evaluate patients, focus on transient lower esophageal sphincter relaxation (TLESRs), tone of lower esophageal sphincter, and anatomic disruptions; TLESRs are normal physiologic relaxations of lower esophageal sphincter to allow air venting, but can result in GERD when associated with acid regurgitation

Lifestyle factors: minority of patients have hypotensive lower esophageal sphincter at rest; can be result of lifestyle factors; foods (fat, chocolate, peppermint, caffeine, alcohol, smoking), and drugs (anticholinergics, nitrates, calcium channel blockers, tricyclic antidepressants, opioids, diazepam, barbiturates), as well as postprandial gastric distension can all induce lower esophageal sphincter hypotension and result in reflux

Anatomic factors: mismatch between lower esophageal sphincter and diaphragm, commonly known as hiatal hernia, can cause reflux; physiologic maintenance of anti-reflux barrier is accomplished by both intrinsic muscles of lower esophageal sphincter, namely longitudinal and circular muscles of esophagus, and diaphragmatic crus that encircles lower esophageal sphincter; when intrinsic muscles of lower esophageal sphincter slide upward, as in hiatal hernia, acid reflux may occur and can be exacerbated by lifestyle factors

Treatment: proton-pump inhibitors (PPIs), H2 blockers, and antacids mainstays of treatment, but usually gastric acid is not cause of GERD, so first assess frequency and severity of symptoms; mild, intermittent symptoms occurring less than twice a week respond well to on-demand therapy with H2 blockers and lifestyle changes; lecturer tends to recommend lifestyle changes first; lifestyle and dietary measures include weight loss for patients with GERD who are overweight or have had recent, large weight gain, elevation of head of bed in patients with laryngeal symptoms, such as cough, hoarseness, frequent throat clearing, or in patients with most symptoms at bedtime; selective elimination of certain dietary triggers, such as fatty foods, caffeine, chocolate, spicy foods, carbonated beverages, peppermint, in patients who have noted their correlation with GERD symptoms and improvement of symptoms with elimination; no need to eliminate all these foods and beverages if symptoms don't improve with elimination or no association is found between foods and symptoms;

Other helpful measures in some patients (study results mixed): avoidance of tight-fitting garments to prevent increased intragastric pressure; promote salivation with use of lozenges and chewing gum, as saliva contains a lot of bicarbonate, which can help neutralize refluxed acid; avoidance of tobacco and alcohol, as both reduce lower esophageal sphincter pressure; abdominal breathing exercises to strengthen anti-reflux barrier in lower esophageal sphincter; for patients who fail lifestyle measures and have typical GERD symptoms, such as heartburn and regurgitation, proton-pump inhibitor therapy should be started, given 30 min prior to morning meals

Testing: *H. pylori* is not cause of GERD; no need for routine testing for *H. pylori*; in absence of alarm symptoms, response to therapy is diagnostic of GERD; no additional testing required; endoscopy indicated in presence of alarm symptoms, such as new onset of dyspepsia in patient >60 yrs, evidence of GI bleeding, iron deficiency anemia, anorexia, weight loss, dysphagia, odynophagia, persistent vomiting, presence of GI cancer in first-degree relative, or failure of patient to respond to treatment

Barrett's esophagus: upper endoscopy used in GERD to screen for Barrett's esophagus; complication of long-term acid exposure in distal esophagus, which is thought to cause metaplastic changes at point where mucosa changes from squamous to columnar epithelium; change in cell types in body or repeated injury and inflammation leads to increased risk for cancer; cancer in Barrett's esophagus follows dysplasia-carcinoma sequence (low-grade dysplasia, followed by high-grade dysplasia, followed by carcinoma); screening advised for patients with certain criteria; men with reflux for over 5 yrs and 2 or more risk factors; risk factors for esophageal adenocarcinoma or Barrett's esophagus include individuals >50 yrs of age, Caucasian race, central obesity (waist circumference >102 cm), current or past history of smoking, confirmed family history of Barrett's esophagus or esophageal adenocarcinoma; routine screening not recommended in women unless multiple risk factors are present

Treatment: focus is primarily on prevention of progression to cancer; recommendation of PPIs in all patients with Barrett's esophagus, regardless of presence of symptoms; surveillance every 3 to 5 yrs with biopsies every 2 cm and separate samples if mucosal abnormalities noted; if dysplasia, either high-grade or low-grade, is present, endoscopic treatment with radiofrequency ablation is performed; shown to treat dysplasia and to cure Barrett's esophagus; esophagectomy used only in patients with cancer or in patients who decline endoscopic therapy, given its morbidity

Dyspepsia

Diagnosis: presents with upper discomfort, sometimes associated with nausea and early satiety; differential diagnosis includes functional dyspepsia, GERD, *H. pylori*-associated gastritis, peptic ulcer disease, gallstones, malignancy; 75% of patients with dyspeptic symptoms have functional dyspepsia without obvious underlying

cause of symptoms; good history important for diagnosis; dyspeptic symptoms with regurgitation or heartburn suggests GERD; pain in right-upper quadrant lasting 30 min after eating suggests gallstone disease; endoscopy recommended in all patients >60 yr of age with new onset symptoms to exclude malignancy; *H. pylori* testing is recommended if no etiology of symptoms is found; routinely stool testing, but also breath testing; patients need to be off PPIs and have no recent antibiotic exposure, as both decrease sensitivity of test; antibodies to *H. pylori* are rarely tested because positive test does not suggest active disease; if patient is *H. pylori*-positive, treat and confirm eradication; if patient is *H. pylori*-negative, or symptoms persist after eradication, can do empiric trial of PPIs for 1 or 2 mo; if symptoms persist, diagnosis of functional dyspepsia is made; next step is trial of tricyclic antidepressant, such as amitriptyline; if symptoms still persist, guidelines call for trial of prokinetics; important to discuss extrapyramidal side effects with patient; upper endoscopy often done at this point to exclude organic cause of symptoms in patient who has failed trial of PPI, is *H. pylori*-negative, and has failed trial of tricyclic antidepressant; endoscopy should only be performed in patients with refractory symptoms, patients >60 yrs of age, or patients with alarm symptoms, such as rapid progression of disease, weight loss, dysphagia, odynophagia, anemia, bleeding, palpable mass, or history or family history of GI malignancy

Peptic ulcer disease: can present with dyspeptic symptoms; most common causes are *H. pylori* and NSAIDs; disease incidence highest when both present; *H. pylori* exclusively colonizes gastric epithelium, is adapted to acidic environment of stomach; when patient is chronically infected, acid secretion is stimulated, while protective mucous layer of stomach is degraded; NSAIDs also diminish mucous layer through inhibitory effects on prostaglandin synthesis; with this combination of factors, decreased mucous layer and increased acid secretion, ulcers may develop; endoscopy diagnostic test of choice in patients with these risk factors and dyspeptic symptoms; urgent evaluation needed in presence of anemia or gastrointestinal bleeding, either vomiting blood (hematemesis), or passing blood in the stool, either hematochezia or melena; endoscopy is used both to diagnose peptic ulcer disease and to treat any high-risk stigmata of bleeding; all patients with peptic ulcer disease should be tested for *H. pylori* by biopsy at time of endoscopy, stool antigen testing, or breath testing; treatment of *H. pylori*-positive patients with combination of 2 antibiotics and a PPI; after treatment, testing done to confirm eradication; patient must be off antibiotics for at least 1 mo and PPI for at least 1 wk; confirmation of eradication important because 25% of patients will remain positive and need second course of treatment; patients with NSAID-induced peptic ulcer disease and negative *H. pylori* test should avoid NSAIDs; if NSAIDs are needed, should be given in combination with PPI; all patients with peptic ulcer disease should receive twice-daily PPI for 8 wks; if gastric ulcers were present, follow-up upper endoscopy in 6 to 8 wks needed to confirm ulcer healing; biopsy should be done to exclude malignancy of ulceration

Gastric cancer: chronic infection with *H. pylori* can result in chronic gastritis and atrophic gastritis, believed to be early changes in progression to gastric adenocarcinoma; high degree of suspicion needed, as gastric cancer can present insidiously; early endoscopy indicated for dyspepsia in patients with family history of gastric cancer, weight loss, bleeding, or iron deficiency anemia; early treatment of gastric cancer can be done endoscopically; for advanced cases, surgery or palliative care may be needed; other environmental factors in development of gastric cancer, besides *H. pylori*, are diets rich in salt and nitrates, obesity, and tobacco use

Gastric polyps: very commonly encountered in endoscopy, usually not malignant; fundic gland polyp most common type, associated with familial adenomatous polyposis and other conditions, but most often associated with PPI use; almost no malignant potential; biopsied to confirm visual diagnosis; if confirmed, no routine surveillance necessary; hyperplastic polyp has malignant potential, can grow large and result in bleeding, should be removal at time of initial endoscopy or at follow-up endoscopy after biopsy

Subepithelial lesions in stomach: most common are benign leiomyomas and gastrointestinal stromal tumors; diagnosed with endoscopic ultrasound, lesions emanate from outer muscular layer of stomach; leiomyomas typically benign, do not need to be removed; gastrointestinal stromal tumors have malignant potential, should be removed in appropriate cases; difficult to separate leiomyomas from gastrointestinal stromal tumors on ultrasound, so most of these lesions will be removed surgically

Gastroparesis: common complication in patients with diabetes, more than 65% of diabetes patients with upper GI complaints have delayed gastric emptying; other causes of gastroparesis are viral infections, medications, autoimmune diseases; idiopathic cases exist; symptoms are post-prandial nausea, vomiting that contains undigested food from previous meals, and abdominal pain; upper endoscopy or barium study indicated to exclude gastric outlet obstruction from ulcer or tumor, which may present similarly to gastroparesis but is managed very differently; once obstruction excluded, should perform gastric emptying study using gastric scintigraphy; if gastroparesis found in patient without diabetes, workup includes fasting glucose test to exclude undiagnosed diabetes, thyroid-stimulating hormone (TSH) test to exclude hypothyroidism, as well as antinuclear antibody (ANA) test to exclude autoimmune disease; many patients with delayed gastric emptying can be treated with dietary modification; low residue, low-fiber diet changed to liquid diet during flares to allow emptying of residual food material in stomach; after few days of liquid diet, reintroduce food; some patients will require pharmacologic therapy, which includes erythromycin, a good prokinetic, but patients quickly develop tachyphylaxis; also medical loperamide, effective, but risk of developing tardive dyskinesia (TD); non-pharmacologic options few; include placement of gastric pacemaker, although not widely available or reimbursed by insurance; renewed interest in pyloromyotomy with advanced endoscopic tunneling techniques to selectively cut the muscles of pylorus, which results in improved gastric emptying

Gastric bypass surgery: most commonly performed obesity surgery in US in last decade was Roux-en-Y gastric bypass; recently eclipsed by gastric sleeve operation; traditional Roux-en-Y gastric bypass operation creates small gastric pouch, which is attached to jejunum, excluding stomach and duodenum; iron deficiency

may develop because of decreased iron absorption in duodenum; also because of the anatomic modifications, there is decrease in exposure of food to stomach and decreased mixing of food with pancreatic secretions, leading to B-12 malabsorption, which is exacerbated by diminished production of intrinsic factor and decreased release of B-12 from salivary R-protein; positive effects of Roux-en-Y gastric bypass are restriction of amount of food patient can eat due to small gastric pouch, delivery of undigested food deeper into small bowel, resulting in release of glucagon-like-peptide-1 (GLP-1) and peptide YY (PYY), which induce satiety and improve glucose tolerance; since duodenum is bypassed, secretion of gastric inhibitory polypeptide (GIP), a hormone associated with weight gain, is decreased; potential negative effects and complications of gastric bypass include early satiety, nausea, dumping syndrome, ulcerations at anastomosis, which may require intervention, fistulas to the excluded stomach, which may result in weight gain, or enlargement of pouch or anastomosis, which may also result in weight gain

Gastrointestinal bleeding: patients with upper GI bleeding present with melenic stools and alteration of vital signs, of which hypotension and tachycardia are most concerning; diseases causing GI bleeding range from less severe, such as esophagitis, Mallory-Weiss tear from retching and vomiting, gastric erosions, and angioectasias, to most severe, such as gastric cancer, Dieulafoy lesion, esophageal varices, peptic ulcers; mortality in gastrointestinal bleeding mainly depends on patients' comorbidities rather than underlying cause; initial management should focus on resuscitation with fluids and blood products and the use of PPIs; octreotide is used when varices are suspected; majority of patients need to be admitted to hospital for endoscopy; a few young patients with normal vital signs and normal blood counts can be managed in outpatient setting; endoscopy to determine cause of bleeding, but also to provide treatment and stratify the risk of re-bleeding; if variceal bleeding, band ligation can stop bleeding and prevent future bleeding; in peptic ulcer disease with high-risk stigmata such as visible vessel, spurting vessel, or active oozing, treatment is with epinephrine, clipping, and electrocautery to stop bleeding and decrease risk of re-bleeding; test all patients with peptic ulcer disease for *H. pylori* and treat those who test positive; avoid NSAIDs if possible; if patient needs to remain on NSAIDs, such as patient with cardiac stent needing long-term high-dose aspirin, pair NSAIDs with PPIs to minimize risk of re-bleeding

Suggested Reading

Feld L et al: Management of dyspepsia. *JAMA* 2018 May;319(17):1816-7; **Johnston BT:** Oesophageal dysphagia: a stepwise approach to diagnosis and management. *Lancet Gastroenterol Hepatol* Aug 2017;2(8):604-9; **Talley NJ et al:** Functional dyspepsia. *N Engl J Med* 2015 Nov;373(19):1853-63; **Triadafilopoulos G et al:** Precision GERD management for the 21st century. *Dis Esophagus* 2017 Sep;30(9):1-6.

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Common Gastrointestinal Disorders Seen in Outpatient and Inpatient Settings

Christopher Marshall, MD, *Assistant Professor, Division of Gastroenterology, University of Massachusetts Medical School*

Acute pancreatitis: one of the most common gastrointestinal (GI) diagnoses at discharge; estimated annual cost in 2009 of $2.6 billion; if managed poorly, can lead to poor outcomes and prolonged hospital stays;

Diagnosis: typically straightforward; made by history, physical exam, and simple lab tests; often no need for diagnostic imaging; American College of Gastroenterology guidelines state diagnosis requires 2 of the 3 following criteria: 1) typical symptoms, including upper abdominal pain radiating to the back or flanks, 2) elevated amylase or lipase >3 times upper limits of normal, 3) characteristic findings on imaging; early imaging reserved for unclear diagnosis

Treatment: aggressive isotonic intravenous (IV) hydration 200-500 mL/hr, unless comorbidities such as cardiac or renal disease; urine output should guide fluid management for first 24 hrs; recent trend towards early feeding; newer studies suggest that for mild acute pancreatitis early feeding (*ie*, before pain resolves, but once improvement is seen) with clear or low-fat diet is safe; also, enteral feeding via nasogastric tube or nasojejunal tube is safe and preferred over parenteral nutrition in patients with severe acute pancreatitis; can decrease GI translocation of bacteria and infectious complications

Severity: no perfect scoring system for acute pancreatitis to predict severity at time of admission; most scoring systems require 48 to 72 hrs for accuracy; thus, examination to assess early fluid losses, hypovolemic shock, and symptoms suggestive of organ dysfunction is crucial; elevated hematocrit >44% and blood urea nitrogen (BUN) >20 mg/dL that either rises or fails to decrease with fluid rehydration predict poor prognosis, indicative of hemoconcentration and under-resuscitation

Imaging: computed tomography (CT) scan or magnetic resonance imaging (MRI) in patients with severe disease, worsening over 48-72 hrs, can determine presence of necrosis, predict outcomes, and prognosis

Etiology: gallstones and/or alcohol in majority of cases; as gallstones leading cause, important to evaluate right upper quadrant ultrasound on all patients; if gallstones, refer for cholecystectomy; alcohol only considered in patients with heavy alcohol history (*ie*, >50 g/day for >5 yrs); medications less common etiology (eg, azathioprine, especially if recently started); if testing/history is negative, evaluate serum triglyceride level; >1000 mg/dL associated with acute pancreatitis; in patients >40 yrs, consider benign and malignant pancreatic tumors, which can occasionally present as acute pancreatitis; contrast-enhanced CT scan or MRI after acute episode of pancreatitis resolves will diagnose tumors; if recurrent pancreatitis or high suspicion for tumor, consider endoscopic ultrasound

Chronic pancreatitis: can occur with repeated injury to the pancreas, either as distinct episodes of acute pancreatitis or subclinical indolent injury; leads to impairment of pancreatic bicarbonate secretion,89 which results in proteinaceous plugs within pancreas and stones and/or ductal obstruction; also intra-parenchymal activation of pancreatic enzymes, due to genetic alterations or genetic susceptibility and repeated injury; majority of cases due to alcohol abuse, genetic causes (*eg*, mutations in the cystic fibrosis gene), hereditary pancreatitis, ductal obstruction (*eg*, trauma, cysts, stones, tumors, and pancreas divisum), tropical pancreatitis, systemic diseases (*eg*, systemic lupus erythematosis, hypertriglyceridemia, hyperparathyroidism), autoimmune conditions (eg, autoimmune pancreatitis), idiopathic pancreatitis, and cigarette smoking; typically present with chronic abdominal pain; may also have signs of exocrine pancreatic insufficiency such as fatty diarrhea and weight loss; late in disease course, may develop endocrine pancreatic insufficiency (eg, diabetes); other complications include pseudocyst formation, bile duct or duodenal obstruction, pancreatic ascites, pleural effusion, splenic vein thrombosis, pseudoaneurysms, and pancreatic cancer

Treatment: focused on decreasing injury and pancreatic stimulation; advise patients to quit smoking, stop drinking alcohol, eat small, frequent, low-fat meals; prescribe pancreatic enzyme supplementation to suppress exocrine enzyme secretion; if no improvement, endoscopic nerve blocks, endoscopic retrograde cholangiopancreatography (ERCP) for pancreatic stones, or surgery

Autoimmune pancreatitis: autoimmune inflammation of pancreas; may result in recurrent acute pancreatitis or chronic pancreatitis; may be associated with variety of autoimmune diseases, but predominately an IgG4 disease; can manifest as recurrent abdominal pain, pancreatic ductal strictures, or pancreatic mass, mimicking pancreatic cancer; inflammation may also result in biliary obstruction; diagnosis often made by characteristic findings on imaging (*eg*, "sausage-shaped" pancreas), histology, or presence of elevated IgG4 level; treatment typically with corticosteroids; reserve immunomodulary drugs (*eg*, azathioprine) for relapse

Pancreatic cysts: common incidental findings in up to 2% of imaging studies; fifty percent cystic neoplasms;

serous subtypes have low malignancy potential; mucinous type, solid pseudopapillary tumors, and some intra-ductal papillary mucinous tumors have malignancy potential; cysts require close observation by imaging or endoscopic ultrasound; resection if >3 cm, have solid component, associated with acute pancreatitis, or associated with dilated pancreatic duct, because these features suggestive of early malignant transformation

Pancreatic cancer: fourth leading cause of cancer-related death in the US; often indolent; typical presentation abdominal pain, obstructive jaundice, and weight loss; most patients have nonspecific symptoms and often present late in disease course; surgery only known cure

Causes: hereditary and non-hereditary; controllable causes include cigarette use, high-caloric diet, obesity, physical inactivity

Staging: CT scan for staging and, most important, to determine resectability, evaluates features including distal disease and invasion of abdominal vasculature; endoscopic ultrasound provides similar information and allows for biopsy of tumor and local lymph nodes

Cancer types: pancreatic adenocarcinoma not the only neoplasm in or near the pancreas; obstructive jaundice and weight loss warrant evaluation for cancer at the ampulla, especially if imaging suggests "double duct" sign (*ie*, dilated bile and pancreatic ducts); suggests obstruction at opening of both ducts (ampulla of Vater); ampullary cancer management is endoscopic resection if caught early, but most cases are more advanced and require surgery (*eg*, Whipple procedure); other tumors include neuroendocrine tumors (*ie*, islet cell tumors); tumors of endocrine pancreas often have better prognosis than pancreatic adenocarcinoma; can secrete variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide, resulting in myriad clinical syndromes; note 50%-75% of pancreatic neuroendocrine tumors are nonfunctioning with no hormonal syndrome

Diseases of small bowel and colon

Acute diarrhea: acute diarrhea, <14 days, vs chronic diarrhea, >4 wks; majority of acute diarrhea due to viral causes, typically self-limited; stool studies in these cases usually not necessary, treatment mostly supportive care; most acute diarrhea, even bacterial, will resolve with simple support; stool cultures considered once symptoms present >72 hrs; diagnostic investigation reserved for patients with severe dehydration or illness, persistent fever, persistent bloody stool, immunosuppression, or for cases of suspected nosocomial infection or outbreak; hemorrhagic diarrhea suggests bacterial infection (eg, *Salmonella*, *Shigella*, *Campylobacter*, Shiga toxin-producing *Escherichia coli*, *Clostridium difficile*, *Entamoebae histolytica*, *Yersinia*); stool cultures in the presence of blood have 30% yield; routine stool cultures for watery diarrhea have much lower yield; yield for ova and parasite testing in the US is very low, not routinely done unless symptoms >7 days; antibiotics are not necessary in most patients; most patients will improve on their own; use of antibiotics may result in a prolonged course or more complications; antibiotics warranted for patients >65 yrs, septic, severely ill, or immunocompromised

Chronic diarrhea: more challenging; diarrhea >4 wks; three basic categories are watery, fatty, and inflammatory; watery diarrhea further subdivided into osmotic, secretory, and functional diarrhea; watery diarrhea includes irritable bowel syndrome, most common cause of functional diarrhea; microscopic colitis is watery, secretory diarrhea, typically affecting elderly; laxative-induced diarrhea often osmotic; malabsorptive diarrhea presents with excess gas, steatorrhea, and weight loss (*eg*, giardia infection, exocrine pancreatic insufficiency); celiac disease also malabsorptive, commonly see weight loss and iron deficiency, but not always other typical features of malabsorptive diarrhea; inflammatory diarrhea (*eg*, ulcerative colitis, Crohn's disease) often associated with abdominal pain and elevated fecal calprotectin level

Work-up: detailed history followed by targeted testing based upon the results; *eg*, if symptoms and history suggest infection, perform stool studies; with history suggestive of malabsorption, focus testing accordingly; history suggestive of microscopic colitis or inflammatory bowel disease, colonoscopy next reasonable step

Microscopic colitis: watery, chronic diarrhea; typically secretory; can be severe; common in gastroenterology practice; represents 10% of chronic diarrhea cases; incidence increases with age; can be idiopathic; association with certain medications, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs); diagnose with colonoscopy; mucosa appears endoscopically and macroscopically normal, but biopsy demonstrates microscopic evidence of inflammation; to treat, withdraw offending medication if possible; if not possible, or ineffective, prescribe antidiarrheals (*eg*, loperamide); if this fails, prescribe budesonide, starting at 9 mg for 4 wks, then tapering by 3 mg every 2 wks

Malabsorption: diarrhea worse after meals, fatty, associated with weight loss; variety of diseases, including infection (*eg*, small bowel bacterial overgrowth, giardia, Whipple disease); patients with multiple bowel resections may also have high volume diarrhea due to short-bowel syndrome, may not absorb enough nutrients or water to sustain life, and may require chronic parenteral nutrition

Celiac disease: subset of malabsorption; due to chronic inflammation in proximal small intestine; result of immune reaction to gluten (wheat protein); duodenum is most affected, thus, often an associated iron deficiency; classic presentation is diarrhea, weight loss, and iron deficiency; however, majority of patients not classical, present with nonspecific GI complaints or isolated iron deficiency; diagnosis by tissue transglutaminase (tTG) IgA level; also evaluate total IgA level as many have IgA deficiency (*ie*, may lead to false negative); upper endoscopy to confirm positive cases after gluten challenge, or if diagnosis is unclear

Inflammatory bowel disease (IBD): frequent cause of chronic diarrhea; bimodal age distribution; early peak in children and young adults with second peak late in age; ulcerative colitis affects only the colon, resulting in bloody diarrhea, abdominal pain, and tenesmus; on colonoscopy, patients have continuous disease that starts in the rectum and extends proximally; Crohn's disease can affect mouth to anus, terminal ileum most commonly affected; extra-intestinal manifestations of IBD vary in severity, may be more debilitating than the IBD; some extra-intestinal manifestations parallel disease activity and are managed by managing the IBD

(*eg*, erythema nodosum, episcleritis, Sweet syndrome); other extra-intestinal manifestations flare independently, can be more difficult to control (*eg*, uveitis, pyoderma gangrenosum)

Ulcerative colitis *vs* Crohn's disease: differences in histology and pathobiology; inflammation of ulcerative colitis is typically mucosal until disease severe; inflammation in Crohn's disease is transmural, putting patient at risk for abscesses, strictures, and fistulas

Etiology: unclear; likely "two-hit" phenomenon; genetic predisposition, evidenced by fact that up to 25% have first-degree relative with IBD; also often a trigger (*eg*, infection, diet, obesity); little understanding of triggers, area of research

Diagnosis: typically requires endoscopic evaluation; in ulcerative colitis, colonoscopy is typically diagnostic; findings include continuous nature of disease and the quality of ulcerations; in Crohn's disease, colonoscopy can diagnose if disease is present in colon or terminal ileum; if colonoscopy normal, video capsule endoscopy can be performed; small wireless device that takes up to 6 images per sec as it passes through small intestine; directly images the mucosa, thus, very sensitive for mild disease or disease only involving the mucosa; laboratory testing to measure stool calprotectin (measure of inflammation in bowel), as well as other more systemic inflammatory markers such as C-reactive protein (CRP); test for vitamin micronutrient deficiencies (*eg*, vitamin B_{12}, iron, vitamin D); if a complication is suspected, imaging can be helpful; in general, avoid CT scans to minimize radiation exposure; many IBD patients young, and thus could have heavy radiation exposure over time; MRI enterography test of choice; can diagnose fistulas and abscesses and assess inflammatory and fibrotic strictures; helps in planning therapy

Management: traditionally, therapy "bottom up" (ie, try least effective/cheapest/most benign medications first, proceed to more effective, more expensive, riskier drugs if initial treatments ineffective); in this scheme, might start with antibiotics or mesalamine; if no improvement, transition to corticosteroids; typically, when patients start corticosteroids, immunomodulator therapy is then used, and corticosteroids discontinued; if patients fail immunomodulators, transition to biologic therapy; biologics are group of injectable medications active against substances within the inflammatory cascade (*eg*, antibodies to tumor necrosis factor (TNF) alpha, and medications against interleukin-12 (IL-12), IL-23, or leukocyte adhesion molecules); recently, "top down" approach being used (*ie*, start with biologics, then step down therapy once disease is under control), proven beneficial for high-risk patients, *ie*, those at risk for developing complications such as perforating, penetrating, fistulizing, or long segments of IBD, patients with history of 2 or more surgeries for Crohn's disease, patients with rapidly progressive course of Crohn's disease; gastroenterologist and internist should work together on managing IBD patients; patients at increased risk for infections due to underlying disease, malnutrition, previous surgery, and immunosuppressive medications; thus, routine vaccination status should be evaluated at time of diagnosis (*eg*, influenza and pneumococcal vaccines); live vaccines contraindicated in patients on immnosuppressives; patients also at increased risk for colorectal cancer, require surveillance colonoscopy; women with IBD on corticosteroids and immunosuppressants at higher risk for cervical cancer, require annual cervical cancer screening while on these medications; all patients taking or previously on immunomodulators or biologics require annual skin examinations as melanoma and other non-melanoma skin malignancies are associated with certain immunosuppressants; increased risk for bone loss with frequent use of corticosteroids, thus screening for osteoporosis should be also be performed at diagnosis and periodically thereafter

Constipation: great majority affected have chronic slow transit constipation; diseases associated with constipation include neurologic and metabolic diseases, obstructing lesions of the GI tract (*eg*, colorectal cancer), endocrine disorders (*eg*, diabetes, hypothyroidism), psychiatric disorders (*eg*, anorexia), medications (*eg*, opiates, antihistamines, antidepressants, antispasmodics, calcium channel blockers); dyssynergic defecation is functional outlet disorder in which puborectalis muscle paradoxically contracts rather than relaxing during defecation; diagnosis can often be made with history and physical exam, in which can sometimes appreciate narrowing of rectal angle during simulated defecation; in majority of cases of chronic constipation limited role for routine lab evaluation, imaging, or endoscopy; reserve evaluation for patients with "alarm features" such as hematochezia, weight loss of >10 pounds, family history of colon cancer or IBD, anemia, positive fecal occult blood tests, or acute onset in elderly patient

Chronic idiopathic constipation: management with increased fluids and fiber; if no improvement, consider over-the-counter fiber supplements (*eg*, psyllium); polyethylene glycol taken daily is typical next step; osmotic agent which increases colonic fluid content; safe, effective, non-habit forming; effectiveness can be improved if paired with stimulant laxative (*eg*, bisacodyl, Senokot); newer, effective medications include linaclotide and plecanatide, which encourage intestinal water secretion and transit through stimulation of guanylate cyclase receptors; lubiprostone stimulates fluid secretion via activation of chloride channels

Dyssynergic defecation: management via biofeedback; work with a specialist to retrain puborectalis muscle

Opioid-induced: switch to peripherally acting mu opioid receptor antagonists; block effects on mu opioid receptors in intestines; methylnaltrexone or naloxegol

Irritable bowel syndrome (IBS): functional disorder; characterized by chronic abdominal pain and altered bowel habits; up to 50% of GI referrals; history alone typically adequate for diagnosis; further investigation warranted for new onset of IBS symptoms, age >50 yrs, rectal bleeding, nocturnal diarrhea, progressive abdominal pain, unexplained weight loss, lab abnormalities (*eg*, iron-deficiency anemia, elevated inflammatory markers, or elevated calprotectin), family history of IBD or colorectal cancer (possible genetic predisposition)

Rome criteria: set of criteria to aid in diagnosis and classification of IBS; Rome IV criteria (newest) defines IBS as recurrent abdominal pain on average at least 1 day per wk in the last 3 mo, associated with 2 or more of the following criteria: pain occuring with defecation,

change in stool frequency, or change in stool form/appearance; note that many IBS patients do not meet these criteria;

Compassionate approach to management: treatment often best when given by compassionate provider who listens to the patient, sets realistic goals of therapy, avoids sending mixed messages on testing, and recognizes and addresses patient's hidden fears (*eg*, concern for cancer, inflammatory bowel disease, or other disorders)

Diet: history may reveal patterns of symptoms related to specific foods; patients may benefit from exclusion of gas-producing foods, or from diets low in fermentable oligo-, di- and monosaccharides and polyols (FODMAPs) and in some cases lactose and gluten avoidance; dietary measures should be investigated prior to pharmacologic treatment

Pharmacologic management: treat symptoms; fiber effective for diarrhea and constipation; antispasmodics or low-dose antidepressants (*eg*, amitriptyline) for pain; antidiarrheal (*eg*, loperamide) if diarrhea is predominant; polyethylene glycol used for constipation-predominant cases; can use guanylate cyclase receptor antagonists and calcium channel activators if polyethylene glycol ineffective

Diverticulosis: common finding in asymptomatic patients; seen in upwards of 50% of colonoscopies in some populations; frequency increases with age; diverticulosis means only presence of diverticula; diverticular disease refers to patients who have symptomatic diverticulosis; infected diverticula termed diverticulitis; diverticula form commonly at sites of penetration of major branches of vasa recta through the circular muscle; mucosa herniates through these weaknesses because of increased intraluminal pressure (typically because of diminished stool volume due to low-fiber diet and increased colonic contractions to move stool from one segment to another); diverticulitis due to stasis or impaction of the diverticulum; results in left lower quadrant abdominal pain, possibly also fever and obstipation; uncomplicated diverticulitis typically resolves with antibiotics, although patients with more severe disease, such as abscess and fistulization may require surgery; diverticular bleeding can be complication of diverticulosis; common cause of lower GI bleeding; typically painless and self-limiting; ongoing bleeding may require endoscopic or radiographic hemostasis, rarely surgery; diverticular disease may also present with left lower quadrant spasm, which sometimes mimics diverticulitis; majority managed with increased fluids, fiber, and antispasmodics, rarely need resection

GI vascular disease: GI tract has rich blood supply; celiac artery supplies foregut (stomach, proximal duodenum); superior mesenteric artery supplies midgut (small intestine to splenic flexure of colon); inferior mesenteric artery supplies hindgut (left colon, rectum)

Acute mesenteric ischemia: surgical emergency; acute occlusion of mesenteric vessel or its branches, typically superior mesenteric artery because of angulation off aorta; majority are embolic, some cases due to ruptured native atherosclerotic plaque; commonly see acute onset of severe abdominal pain; superior mesenteric artery occlusion symptoms also include nausea, vomiting; important principle of management is recognition; rule out in any case of severe abdominal pain; initial management involves resuscitation with fluids; anticoagulation if embolic disease; most cases require surgical exploration; ischemia may also occur due to small intestinal hypoperfusion secondary to diminished blood flow; can occur in sepsis, heart failure, and vasoconstrictor use; initial management is treating underlying cause and eliminating vasoconstrictors; may progress and need resection

Colonic ischemia: uncommon for embolic disease to result in ischemia of the colon; great majority related to hypoperfusion; typically develop in "watershed" areas (*ie*, overlap of blood supply from 2 different vascular territories); commonly splenic flexure and rectosigmoid colon; typical presentation is abdominal pain and bleeding; imaging will show thickening and inflammation; diagnosis typically made by colonoscopy

Chronic mesenteric ischemia: different clinical entity from acute; due to chronic low blood flow to intestinal tract during meals, usually because of narrowing within mesenteric vessels; need critical stenoses of 2 abdominal vessels for diagnosis; typical symptoms are postprandial abdominal pain, "food fear" (patient doesn't want to eat), weight loss; management through modifying risk factors to decrease progression of disease; stenting of abdominal vessels if severe

Anorectal disorders: common outpatient issue; present in variety of ways; itching (pruritus ani) due to systemic illnesses (*eg*, thyroid disease or diabetes), infection (*eg*, pinworms), but most commonly caused by hemorrhoids, fecal incontinence, constipation, fistula, fissures, or over-vigorous cleansing; anal pain, another common complaint, requires history focusing on nature of pain and relationship to bowel movements; aching after bowel movement can occur with internal hemorrhoids; acute onset of pain and palpable mass likely thrombosed external hemorrhoid; this intense pain usually lasts 48-72 hrs and subsides spontaneously; sharp pain and bleeding typically due to anal fissure; diagnosis usually made by history and confirmed by digital rectal exam

Fecal incontinence: prevalence of approximately 7%; defined as loss of sold or liquid feces; further subdivided into urge incontinence (*ie*, urge to defecate prior to episodes) and passive incontinence (*ie*, occurs without patient awareness); usually due to coexistence of multiple reasons; *eg*, anal sphincter weakness due to a traumatic childbirth, combined with spinal disease, anal surgery for fistula, or hemorrhoids; decreased perception of rectal distention can occur in diabetes, multiple sclerosis, and dementia; patients with chronic inflammation of the rectum may have decreased rectal compliance, resulting in fecal incontinence; can occur with ulcerative colitis or radiation proctitis; overflow incontinence can occur in presence of hard, impacted stool, when only liquid stool can move past; diagnosis requires good history and perianal examination; additional testing includes anorectal manometry for sphincter weakness or sigmoidoscopy for inflammation

Anal cancer: uncommon; less than 3% of GI malignancies; increased incidence with female gender, human papilloma virus (HPV) infection, increased lifetime number of sexual partners, genital warts, cigarette smoking, receptive anal intercourse, human immunodeficiency virus (HIV) infection, and other chronic immunosuppression; no formal recommendations for screening; patients at risk should be

made aware of symptoms and how to modify risks, and have a digital rectal exam

Lower GI bleeding: approximately 20% of GI bleeding; once defined as bleeding beyond ligament of Treitz, but small bowel bleeding is now separate category not discussed in this lecture; for this lecture, lower GI bleeding defined as bleeding within the GI tract from the colon through the anus; majority of patients with acute lower GI bleeding will present with hematochezia (bright red blood from the rectum); note that bleeding from the right colon may present with melena, especially if the bleeding is slow and intermittent; also note that vast majority of patients with hematochezia will have a lower GI bleed, but up to 15% will actually have brisk upper GI bleed; important to recognize these patients, as often have high mortality; brisk upper GI bleed clues are significant hemodynamic changes such as hypotension, tachycardia, significant orthostasis, or history of syncope or pre-syncope

- Diverticular bleeding: most common cause of lower GI bleeding in adults; bleeding often brisk and painless; may have history of diverticulosis on imaging or colonoscopy
- Colitis: presents with pain and bleeding; can be due to inflammatory bowel disease, ischemia, or infection
- Angioectasias: may present as melenic stool if in right colon, or as hematochezia; can also result in occult blood loss and chronic iron-deficiency anemia
- Cancer and polyps: may present with occult bleeding if in right colon; can also present with overt hematochezia if in right or left colon
- Hemorrhoidal bleeding: common; large volume or trickle of bright red blood coming from the rectum
- Initial management and diagnostics: supportive; if patient anemic, blood products should be given; coagulopathies should also be addressed; resuscitation should be provided with goal of normalizing blood pressure and heart rate prior to any endoscopic evaluation; recent change in thinking about discontinuation of anticoagulants in presence of bleeding; note that anticoagulants rarely cause bleeding, but can exacerbate existing causes; important because many anticoagulants cannot be safely discontinued, thus, perform endoscopy with hemostasis in patients who are therapeutically anticoagulated and reserve reversal of anticoagulation for patients whose anticoagulation is supertherapeutic or who have severe or life-threatening bleeding; brisk upper GI bleeding requires endoscopy to exclude peptic ulcer disease; in all other patients, once stabilized, a colonoscopy (after bowel purge) can be performed; patients who can be discharged without inpatient colonoscopy for later outpatient colonoscopy are age <60 yrs, present with normal hemodynamics and blood counts, have stopped bleeding or bleeding is suspected to have an anal source (*eg*, hemorrhoids or anal fissures); colonoscopy helps to localize the bleeding and also allows for management with clipping or injection if needed

Colorectal cancer: third most common cause of cancer death among women; second most common cause of cancer death among men; smoking, obesity, diets rich in red and processed meats, and alcohol are modifiable risk factors; non-modifiable risk factors include age, family history of colorectal cancer, polyposis syndromes, history of polyps, and inflammatory bowel disease

- Presentation: some present with occult blood loss, especially if tumor is in right colon; tumors in left colon may present with occult blood loss or overt bleeding and a change of bowel habits; abdominal pain and weight loss less common features
- Colonoscopy: primary means of diagnosis; allows for tissue acquisition as well as palliative therapy (*eg*, stents if obstruction) is present; important role in prevention because allows detection and resection of polyps (precursors to colorectal cancer); other screening modalities (*eg*, fecal DNA and virtual colonoscopy) can detect cancer and polyps, but do not allow for immediate resection; average-risk patients need colonoscopy at age 50 yrs, repeated every 10 yrs; newer guidelines state incidence of colorectal cancer in younger patients is increasing and recommend screening patients earlier; if family history (*ie*, first-degree relative with colon cancer age <60 yrs, or 2 second-degree relatives regardless of age), screen beginning at age 40 yrs or 10 years younger than index case; repeat every 5 yrs; if polyps, colonoscopy recommended every 5 yrs, although may perform more frequently based on number of polyps, typically, 3 or more polyps or the histology of the polyps; for villous component polyps, higher risk of colon cancer, so perform colonoscopy every 3 yrs
- Staging: directs management; history, physical exam, chest imaging, and abdominal CT scan; routine positron emission tomography (PET) scan not necessary; pelvic MRI and transrectal ultrasound may provide more precise staging
- Lynch syndrome (hereditary nonpolyposis colorectal cancer): high risk for colorectal cancer; accounts for 3% of all colonic adenocarcinomas; mutation in mismatch repair gene; tumors often present at earlier age, with right-sided predominance; often history of extra-colonic tumors in family (*eg*, endometrial, ovarian, stomach, small bowel, hepatobiliary system, brain, renal pelvis, ureter, breast, or prostate tumors); recognizing risk directs further testing and frequency of colonoscopy and other screening tests to look for extra-colonic malignancies or precursor lesions; Amsterdam Criteria and 3-2-1 rule aid recognition- 3-2-1 rule applies to patient with 3 family members with colon cancer or a Lynch-associated cancer, history spanning 2 generations, and affecting 1 relative <50 yrs of age; colonoscopy should begin at age 20-25 yrs, then every 1-2 yrs
- Familial adenomatous polyposis syndrome (FAP): another familial colon cancer syndrome; adenomatous polyposis coli (APC) gene mutation; present with many polyps starting at childhood; colon cancer develops in 90% of untreated patients by age 45 yrs; recommend annual colonoscopies starting at age 10-12 yrs, and continue until colectomy; if family history of FAP, annual colonoscopy should continue until age 40 yrs, and stopped if no polyps have been found
- Inflammatory bowel disease: ulcerative colitis is risk factor for colon cancer; chronic inflammation of the GI tract may trigger colon cancer; patients should have regular surveillance, although recommended intervals vary; patients with extensive colitis or left-sided disease lasting at least 8 yrs should have colonoscopy with routine surveillance biopsies done every 1-3 yrs depending on

guidelines; Crohn's disease that affects at least one-third of colon is risk factor for colon cancer; guidelines for ulcerative colitis should be followed; annual surveillance for high-risk features, which include on-going active inflammation, anatomic abnormalities (*eg*, strictures or pseudopolyps), history of dysplasia, family history of colorectal cancer in first-degree relative, or primary sclerosing cholangitis; if patients have endoscopically and histologically normal mucosa in >2 normal surveillance colonoscopies, interval can be extended

Key Points

1. Many common gastrointestinal disorders can be tentatively diagnosed with a thorough history and physical examination.
2. Acute pancreatitis is one of the most common diagnoses at discharge. Early feeding is a newer treatment method that is gaining favor.
3. Colorectal cancer has a high mortality rate. Regular colonoscopy can prevent development of malignancy.

Suggested Reading

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Approach to the Patient with a Suspected Rheumatologic Disease

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Initial evaluation: lecturer believes that role of primary care provide is first to determine if symptoms are articular or nonarticular, ie, in the joints or in the surrounding connective tissue; for confirmed joint pain, the next step is to differentiate arthritis (inflammatory condition) from arthralgias (non-inflammatory condition) and inflammatory from noninflammatory arthritis, best determined with a detailed joint examination; unfortunately, medical schools and primary care training programs often do not adequately teach structured joint examination, so primary care providers may not be comfortable with performing this exam; if primary care physician is confident that inflammatory arthritis has been ruled out, reasonable to reassure patient and begin discussion of conditions such as osteoarthritis or fibromyalgia, conditions appropriate for treatment by primary care provider

Nonarticular pain: often referred to as "soft tissue rheumatism"; much more common than joint paint; includes various types of neck, shoulder, and low back pain as well as focal soft tissue disorders such as bursitis and tendonitis; the pain is localized, and there may be tenderness at the insertion of a tendon or a ligament or at a bursa; typically no warmth or redness; never any joint swelling;, there can be swelling in a bursa in certain situations such as septic bursitis involving the olecranon or the prepatellar bursa; referral to an orthopedic surgeon or a rheumatologist would be recommended to exclude joint infection

Fibromyalgia

Clinical presentation: generalized, nonarticular pain; present in 3% to 8% of the population; should be strongly considered in any patient who presents with more than 3 months of widespread pain; patients often report that, "I hurt all over," or "I'm always exhausted"; patient often cannot distinguish whether pain is in joints or in periarticular areas; unless there is concurrent arthritis on examination, there is typically no swelling or inflammation of the joints; common finding is tenderness over multiple soft tissue locations rather than over the joints; also associated with prominent fatigue, sleep disturbances, mood disturbances, and headaches; overlaps significantly with other poorly understood but common illnesses including irritable bowel syndrome, chronic headaches, bladder and pelvic pain syndromes, and chronic fatigue syndrome, a group often referred to as functional somatic syndromes;

Laboratory testing: only laboratory testing recommended in clinically suspected case is ESR or CRP; will be normal in fibromyalgia; thyroid function studies should be performed to rule out hypothyroidism, which can cause similar symptoms

Treatment: explore potential sleep and mood disturbances and refer patient to a sleep specialist or mental health professional if appropriate; reassure patient that fibromyalgia is not a crippling disease, though fibromyalgia can cause chronic widespread pain that can interfere with activity; important to have a frank discussion about the role of stress, exercise, and cognitive-behavioral approaches to help maintain an active lifestyle in the patient; medications can be useful; might include simple analgesics or very low dose of a tricyclic antidepressant such as amitriptyline 10 to 30 mg at bedtime which could relieve pain and improve sleep; in patients with more prominent symptoms, a dual reuptake inhibitor such as duloxetine may be effective; for patients with sleep disturbances and widespread pain, an alpha$_2$-delta ligand such as pregabalin is recommended; referral to a physical medicine and rehabilitation specialist and physical therapist could be helpful in planning an ongoing program as well

Lecturer presents clinical case in connection with this condition

Diagnostic testing: the only cost-effective laboratory tests in the evaluation of a patient with suspected rheumatologic disease is the finding of an elevated acute-phase reactant, either the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); patients with osteoarthritis or non-inflammatory soft tissue disorders such as fibromyalgia should always have a normal ESR or CRP; in contrast, in patients with rheumatoid arthritis or any systemic inflammatory disorder, significant elevations should be seen; radiographs may be unremarkable in early rheumatoid arthritis and can be misleading in osteoarthritis since the degree of pain and dysfunction may not correlate well with radiographic changes; radiographs are often best left to the specialist to perform

Testing for systemic rheumatic disease: in primary care, testing for rheumatoid arthritis, systemic lupus erythematosus, or systemic vasculitis should be reserved for patients who exhibit signs and symptoms of multisystem disease; the anti-nuclear antibody (ANA) test has a high prevalence of false positives; low-titer positive ANAs are present in 10% to 15% of healthy individuals, and a low titer positive rheumatoid factor (RF) is almost as common; however, positive ANAs are present in almost 100% of patients with systemic lupus; therefore, their predictive value is best when there is clinical suspicion

of a particular disease; if positive ANA titer is extremely high, or if a positive ANA is associated with more specific serologic tests such as positive anti-double stranded DNA (anti-dsDNA) antibodies, the anti-cyclic citrullinated peptide (CCP) antibody test may help in diagnosis; CCP is more sensitive and specific for rheumatoid arthritis than rheumatoid factor; approximately 70% of rheumatoid arthritis patients will have a positive rheumatoid factor or a positive anti-CCP antibody

Inflammatory versus non-inflammatory arthritis: by definition, any joint swelling implies some form of arthritis; inflammatory arthritis swelling is related to excess synovial fluid and synovial membrane hypertrophy; joint swelling palpates as soft and movable; finding joint effusions in small joints such as the proximal interphalangeal or metacarpophalangeal joints in the hands or in deep ball-and-socket joints such as the shoulders or hips can be difficult; any time joint swelling is associated with warmth and redness you can be sure you are dealing with inflammatory arthritis; swelling in non-inflammatory arthritis is bony in nature and related to structural changes with bone hypertrophy; usually inflammatory arthritis develops quickly, within days or weeks; onset of non-inflammatory arthritis is more insidious, over months or years; tenderness and limited movement in inflammatory arthritis is related to the swelling in the joints, whereas problems moving the joint in non-inflammatory arthritis (osteoarthritis) is related to structural joint changes; inflammatory arthritis is often associated with systemic symptoms such as exhaustion, weight loss, and/or fever; non-inflammatory arthritis is never associated with these systemic signs and symptoms; inflammatory arthritis pain may be relieved with movement or exercise, whereas non-inflammatory arthritis pain is typically worse with joint movement; non-inflammatory arthritis is often associated with cracking upon joint movement, termed "crepitus"

Osteoarthritis: the most common and important form of non-inflammatory arthritis; may involve one or few joints, or may be generalized; typically occurs in patients over the age of 50; prevalence increases dramatically with age; often involves weight-bearing joints, including the knees and hips; also has a predilection for the distal interphalangeal joints of the fingers, the carpometacarpal joints of the thumbs, and the first metatarsophalangeal joint in the big toe; onset is usually gradual; over time, patients develop increased pain and mechanical signs and symptoms such as crepitus or joint locking; morning stiffness may occur but does not last as long as that of inflammatory arthritis; primarily related to wear and tear; increases with age as well as with certain activities such as the development of early ankle arthritis in a soccer player or shoulder or elbow arthritis in a baseball pitcher; some genetic predisposition, so sometimes develops in younger patients or in families

Treatment: discuss efforts at weight reduction if appropriate; non-weight bearing exercise such as water exercise may be helpful; consider referral to a physical therapist; consider trial of anti-inflammatory medications to be taken regularly or trial of celecoxib 200 mg daily; topical nonsteroidal anti-inflammatory agents may be successful in certain cases but potency varies; referral to orthopedic surgeon may be appropriate for those with significant joint damage or symptoms

Lecturer presents clinical case in connection with this condition

Rheumatoid arthritis: although there are more than fifty causes of inflammatory arthritis, rheumatoid arthritis is the most common cause and the prototype for other forms of inflammatory arthritis, such as psoriatic arthritis or arthritis associated with inflammatory bowel disease; key finding is warmth and swelling involving many joints; may begin in few joints then, over time, come to involve the small joints of the hands, feet, wrists, and ankles; carpal tunnel syndrome is common in early rheumatoid arthritis; symptoms often develop quickly and include systemic symptoms; there may be a family history of other immunologic diseases; symptoms usually include severe stiffness, which may last hours at a time; RA is three times more common in women than men; tends to develop between the ages of 30 and 50 years; immediate referral to a rheumatologist is recommended since early rheumatology evaluation and treatment has been noted to improve outcome; obtain limited laboratory testing, including a complete blood count, acute phase reactants, rheumatoid factor or a CCP; radiographs should be left to the discretion of the rheumatologist; extra-articular manifestations in rheumatoid arthritis, in addition to carpal tunnel syndrome, include subcutaneous nodules, usually found over the elbow and extensor forearms, iritis, pleuritis, and pleural effusion

Single hot, swollen joint: any such joint should be immediately aspirated; aspiration of knee (most common site of joint effusion) can be done by primary care provider if he or she is experienced with procedure; aspiration can also be done by rheumatologist or orthopedist; two most common causes of a hot, swollen joint are septic arthritis and crystal-induced arthritis (either gout or pseudogout); causes can only be definitively diagnosed with a joint aspiration; synovial fluid analysis should always be done when joint aspirated for the first time; culture should be done for organisms in suspected septic arthritis; polarizing microscopy should be performed to identify the monosodium urate crystals of gout or the calcium pyrophosphate dihydrate crystals in pseudogout

Septic arthritis: typically includes fever and peripheral blood leukocytosis; acute bacterial arthritis is most often caused by *Staphylococcus aureus*; more common in immune-compromised individuals; disseminated gonococcal infection is more often associated with tenosynovitis and various types of skin rashes; any form of suspected septic arthritis is a relative medical emergency; patient should be seen immediately, when possible by a specialist

Gout: although the only definitive way to diagnose gout or pseudogout is by identifying the appropriate crystals in synovial fluid, this is not always necessary or practical; the abrupt onset of a hot, swollen big toe or ankle or a history of diagnosed gout or classic symptoms of gout is highly suggestive of gout; laboratory findings of an elevated uric acid is helpful for confirming suspected gout diagnosis, but can be misleading; up to 25% to 30% of patients with gout will not have hyperuricemia during an acute gout episode;

Gout treatment, acute**:** if gout is considered clinically likely and joint aspiration and fluid analysis is not practical, appropriate to begin therapy with an anti-inflammatory medicine such as colchicine, prednisone,

or a non-steroidal anti-inflammatory drug; patients with gout usually respond extremely well, and good response supports clinical diagnosis; however, lecturer stresses that for first attack or if large joint involved, aspiration should be done if at all possible; always use adequate dose of anti-inflammatory drug; oral prednisone 3- or 4-day course, starting with 40 mg for first day then gradually tapering; high dose nonsteroidal anti-inflammatory drugs such as naproxen 500 mg twice daily or indomethacin 50 mg 3 times daily are good choices, but should not be used in patients with concurrent renal or cardiovascular disease; colchicine dosing has become more conservative to avoid adverse side effects; recommended dose is 0.6 mg every 6 hours for the first 24 hours followed by rapid tapering; during an acute episode do not use medications to lower the uric acid level as this might aggravate the gout inflammation; only goal of therapy during acute episodes is to decrease inflammation;

Gout treatment, follow-up: following the first episode of gout, even in patients with elevated uric acid levels, another attack may not occur for months or years; recommend lifestyle changes such as weight loss, decreasing alcohol ingestion, and eliminating medications that might increase uric acid, such as diuretics; in a patient who develops recurrent, severe gout or in any patient who has tophi along with gout, medication should be initiated to lower the serum uric acid level; allopurinol is drug of choice; prophylactic medication such as once daily colchicine should be given until the serum uric acid normalizes; target level of serum uric acid <6 mg/dL; allopurinol usually started at 100 mg daily and increased to 300 mg daily until the target uric acid level is attained; adjustment for patients with renal dysfunction is needed; most common side effect of allopurinol is skin rash, which occurs in 3% to 5% of patients; febuxostat is also effective at lowering uric acid; usual dose is 40 mg once daily, but up to 80 mg daily can be used; may be safer choice in patients with renal dysfunction; however, recent study found higher all-cause and cardiac mortality in patients with gout and cardiovascular disease using febuxostat compared to those taking allopurinol

Pseudogout: usually affects the knee, wrist, ankle, or shoulder; typically presents less abruptly than gout, includes less severe inflammation and less pain; occurs more often in older individuals, especially in those with pre-existing osteoarthritis; treatment is similar to that of acute gout with nonsteroidal anti-inflammatory drugs or oral corticosteroids; radiographs may be helpful diagnostically and can demonstrate chondrocalcinosis

Hemarthrosis: another common cause of a hot, swollen joint; "bloody joint"; patient usually should be referred to an orthopedic specialist; there is often a history of significant joint trauma or a pre-existing bleeding disorder

Polymyalgia rheumatica: one of the most common systemic rheumatic diseases seen in primary care; typically occurs in individuals over the age of 60 years; presents with non-specific symptoms, most often severe stiffness (not weakness) involving the proximal muscles of the neck, shoulders, hips, and lower back; physical examination reveals no joint swelling or inflammation; elevated ESR or CRP are typical; there are no other definitive tests; with reasonable clinical suspicion, could prescribe low doses of prednisone such as 10 to 20 mg daily as a therapeutic trial; individuals usually respond extremely well clinically within a few days to corticosteroids; acute phase reactants will fall significantly within a few weeks; if poor response to treatment, an alternative diagnosis should be considered; important to rule out statin-induced myopathy (causes proximal muscle weakness, not stiffness); also important to screen for giant-cell arteritis, as it is often associated with polymyalgia rheumatica and is a medical emergency

Lecturer presents clinical case in connection with this condition

Proximal muscle weakness: differentiate from proximal muscle stiffness; inflammatory muscle disease or statin-induced myopathy common causes; key laboratory finding is elevated muscle enzymes, particularly elevated creatine phosphokinase (CPK); note that isolated elevated CPKs are not unusual and do not always warrant clinical investigation; however, if CPK repeatedly elevated, evaluation for muscle disease should be initiated

Giant cell arteritis: also called temporal arteritis; may present with severe headache, jaw, or scalp pain, visual changes, or non-specific signs such as fever or weight loss; especially important to consider this in patients who have polymyalgia rheumatica; in any older patient with these symptoms, an elevated ESR should prompt referral to a rheumatologist as well as an ophthalmologist for consideration of a temporal artery biopsy; possibility of acute onset of blindness makes consideration of temporal arteritis a medical emergency; if diagnosis seems probable, appropriate to begin high dose oral therapy while awaiting more definitive evaluation

Anti-neutrophil cytoplasmic antibody (ANCA) test: positive test is highly suggestive of Wegener granulomatosis or polyarteritis; for patients with purpura, arthralgias, and unexplained neurologic, cardiovascular, or renal conditions, this laboratory test should be considered

Raynaud phenomenon: history of a biphasic or triphasic color change in digits upon exposure to cold; common in healthy individuals, especially in young women; however, if severe or if dermatologic or systemic symptoms are present concurrently, serologic testing and ideally referral to rheumatologist is recommended; progressive systemic sclerosis (scleroderma) is auto-immune disease that most commonly presents with Raynaud phenomenon predating any other symptoms of the disease for months or years

Key Points

1. The approach to the evaluation of a suspected systemic rheumatologic disorder always starts with differentiating soft tissue rheumatism, either generalized such as with fibromyalgia or localized such as with bursitis or tendonitis, from arthritis.
2. The next step is to determine whether arthritis is inflammatory or non-inflammatory, primarily accomplished by history and a careful joint examination rather than by laboratory testing.
3. The primary screening tests to aid in differential diagnosis are the acute phase reactants. ESR or CRP are almost always elevated in inflammatory disorders and normal in non-inflammatory conditions.
4. The evaluation of any hot, swollen joint is very important in primary care, but depends upon the skill of the

physician in obtaining synovial fluid. A joint aspiration is almost always necessary in a patient with a new onset of a hot swollen joint. However, in the presence of consistent symptoms and patient history, gout can be treated successfully by the primary care physician.

5. Polymyalgia rheumatica is common and responds well to treatment
6. Any patient with evidence of inflammatory polyarticular arthritis or systemic rheumatologic disease should be referred to a rheumatologist.

Suggested Reading

Ameer F et al: Polymyalgia rheumatica: clinical update. *Aust Fam Physician* 2014 Jun;43(6):373-6; **Clauw DJ:** Fibromyalgia: a clinical review. *JAMA* 2014 Apr;311(15):1547-55; **Littlejohn EA et al:** Early diagnosis and treatment ofrheumatoid arthritis. *Prim Care* 2018 Jun;45(2):237-55; **Pereira D et al:** Osteoarthritis. *Acta Med Port* 2015 Jan-Feb;28(1):99-106.

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Arthritis Review

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Osteoarthritis (OA): most common type of arthritis out of >100 types; affects 240 million people worldwide (30 million Americans); more prevalent in developed countries and prevalence increases with age; most common sites hands and knees but can affect any joint; associated with significant morbidity; one of leading contributors to yrs lived with disability

Pathophysiology: previously considered "wear-and-tear" condition, natural part of aging; cause not fully understood, but has been shown to result from combination of biomechanical factors and proinflammatory mediators and proteases; proinflammatory factors drive production of proteolytic enzymes, resulting in progression of OA; pathologic changes include fraying and fibrillation of articular cartilage, thickening of subchondral bone, and formation of osteophytes

Contributing factors: *age* — 14% of adults aged ≥25 yrs and 34% of adults aged ≥65 yrs have symptomatic osteoarthritis; seen on x-ray in persons as early as age 25 yrs; *sex* — more prevalent in females; Framingham Osteoarthritis Study showed 1.7-fold higher incidence of OA of knee in women; gender difference in prevalence less pronounced than in rheumatoid arthritis (RA); *genetics* — influence of genetic factors associated with 30% to 50% of risk of OA, but no clear gene or pathway identified to explain link; *previous injury* — joints with previous injury more likely to develop OA, especially in knee; *biomechanical stresses* — also cause OA; *anatomic abnormalities* — study showed knee OA progressed faster if varus alignment compared with those with valgus alignment; if OA in 1 knee, contralateral knee has higher rate of development of OA partly because of abnormal biomechanical factors from OA in other knee; *obesity* — associated with higher risk of OA, especially in lower-extremity joints; hand joints also increased risk of OA in obese persons; *activities with repetitive motion and heavy physical workload* — associated with increased risk of OA

Types of OA: *primary OA*- occurs in absence of other forms of arthritis; *secondary OA*- develops in presence of another form of arthritis (*eg*, inflammatory arthritis, gout, hemochromatosis, Ehlers-Danlos syndrome, ochronosis, hemoglobinopathy); patients with inflammatory arthritis (*eg*, rheumatoid arthritis [RA] and psoriatic arthritis [PsA]) have higher risk for OA in same joints as those with inflammatory arthritis; inflammatory changes in joints can accelerate development of concomitant OA

Diffuse idiopathic skeletal hyperostosis (DISH): noninflammatory process; development of flowing osteophytes in anterolateral aspect of ≥4 contiguous vertebrae, peripheral enthesitis, and ossification of ligaments and nonvertebral locations on imaging; can be confused with ankylosing spondylitis (AS), but DISH develops in patients aged >50 yrs; more common in men than in women; treated in same way as OA; important to differentiate DISH from AS

Erosive OA: aggressive subset of OA in hand; has inflammatory component; manifests in distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints; not seen in metacarpal phalangeal (MCP) joint or carpometacarpal (CMC) joints; possibility of joint fusion; can be confused on imaging with inflammatory arthritis; treated like OA, not like inflammatory arthritis

Presentation: pain, tenderness, decreased range of motion, bony swelling, joint deformity, joint instability, and morning stiffness <30 mins; starts as sharp and short-lived pain when contact made with joint; over time, more constant pain and stiffness develop; can become dull ache with periods of intense pain; tenderness along joint lines and decreased range of motion of joint; bony swelling can confuse patient, as bony swelling may be resemble swelling; Heberden nodes in DIP joint from osteophyte formation; Bouchard nodes from osteophyte formation at PIP joint; as disease progresses, joint deformity occurs; joint may become unstable; patient may complain of laxity of joint; most common in knees, joints of hands (*eg*, DIP, PIP, first CMC) and feet (*eg*, first MTP), hips, facet joints of cervical and lower lumbar spine; less-commonly affected joints include elbow, wrist, shoulder, and ankle; *gelling phenomenon* — stiffness occurring after period of immobility; after <5 mins, relief of pain long as joint moved

Diagnosis: *imaging*- x-rays most common test; show joint-space narrowing, subchondral sclerosis, cysts; radiographic changes in early OA do not reliably correlate with symptoms; autoantibody testing to rule out RA not necessary if patient has signs and symptoms based on clinical criteria and x-ray findings; role of musculoskeletal ultrasound and magnetic resonance imaging (MRI) in diagnosing OA not defined; *laboratory tests*- synovial fluid analysis not usually needed for diagnosis of OA (if done, expect noninflammatory or mildly inflammatory synovial fluid; <2000 white blood cells [WBCs]/mm^3)

Differential diagnosis:
Inflammatory arthritis: differentiated from OA based on pattern of joints involved, lack of symmetry in OA, lack of associated findings in OA, and presence of morning stiffness such as in RA and PsA not found in OA
Crystal arthropathy: smoldering polyarticular crystal arthropathy can mimic OA; if suspected by history, synovial fluid analysis, blood tests, and x-rays can help differentiate crystal arthropathy from OA
Hemochromatosis: iron overload arthropathy; most common in MCP and wrists; distinct findings on radiographs include squared-off bone ends and hooklike osteophytes; if suspected, get x-rays and blood tests to determine if iron overload
Infectious arthritis: presents with red, warm, swollen joint; if unsure whether infectious arthritis or OA, joint aspiration needed to help determine process causing symptoms
Management: *nonpharmacologic therapy* — first-line treatment for OA; includes exercise, physical therapy (PT), assessment for correctable biomechanical abnormalities, weight loss when applicable; *pharmacologic therapy* — nonsteroidal anti-inflammatory drugs (NSAIDs); topical and oral available; use cautiously in patients with comorbidities such as hypertension, diabetes, or history of or increased risk of gastrointestinal (GI) bleeding; cannot be used in patients taking blood thinners or who have kidney impairment; duloxetine can be used in patients with intolerance to or inadequate response to NSAIDs; prior to starting duloxetine, assess for depression (duloxetine antidepressant medication); if no success with oral or topical medications, intraarticular injections with corticosteroids (almost any joint) or hyaluronic acid (only in the knee) preparations; *surgery* — reserved for patients not successfully treated with medical therapies; total joint replacement most common surgical treatment for OA; most commonly done in knees and hips; arthroscopic debridement of knee not helpful

Spondyloarthritis: group of disorders including AS, PsA, inflammatory bowel disease (IBD)-related arthritis, reactive arthritis, and undifferentiated spondyloarthritis; features include inflammation of axial skeleton, inflammation of tendons and entheses, calcification of tendon can occur; some diseases also include mucocutaneous, GI, and ocular inflammation
Genetic factors: *HLA-B27* — present in 90% of patients with AS; 60% to 70% of patients with reactive arthritis, IBD-associated arthritis, and axial PsA; 25% of patients with PsA without axial involvement; helpful clue, but most people with HLA-B27 do not have spondyloarthropathies, and negative results seen in those with spondyloarthropathies; physical exam and clinical presentation more important than genetic marker
Ankylosing spondylitis: can affect axial skeleton and peripheral joints; also extraarticular manifestations; more common in men than in women (3:1 ratio); peak age of onset in second and third decades; male sex and early age of onset portend poor prognosis
Presentation: inflammatory low-back pain of insidious onset; pain and stiffness worse after immobility, better with use; pain and morning stiffness >1 hr; *skeletal manifestations* — axial involvement, symmetric involvement of sacroiliac (SI) joints progressing up spine (does not skip areas of spine); *peripheral involvement* — enthesitis and asymmetric large-joint oligoarthritis; increased risk of spine fracture because of spinal fragility caused by ankylosing changes; *extraarticular manifestations* — uveitis (typically anterior, unilateral, and recurrent); asymptomatic intestinal ulcerations; urethritis; cardiac manifestations including aortitis, aortic valve disease, conduction abnormalities, coronary artery disease; pulmonary manifestations including apical fibrosis and restrictive lung disease
Physical exam: spine tenderness, SI joint tenderness, limited range of motion of spine, enthesopathy, synovitis
Diagnosis: *laboratory* — complete blood count(CBC), comprehensive panel, sedimentation rate (ESR), and HLA-B27 when applicable; *radiology* — x-rays of SI joints, spine, and peripheral joints; may show erosions, new bone formation, and enthesitis; vertebral changes may include sclerosis at attachment of annulus fibrosis to anterior corner of vertebral endplate and squared vertebral bodies; late x-ray findings include calcification of anterior longitudinal ligament, bridging syndesmophytes (bamboo spine appearance), and new bone formation and changes; at enthesis in SI joint, bilateral and symmetric sacroiliitis; early SI corrosion appears as irregular widening of joint space; sclerotic changes over time lead to fusion and narrowing of SI joints; if x-rays of SI joints and spine negative but suspicious for ankylosing spondylitis, MRI of SI joints warranted
Management: *nonpharmacologic* — initial conservative therapy with exercise and localized glucocorticoid injection; medications usually, if not always, required; *pharmacologic* — NSAIDs for pain control; conventional disease-modifying drugs (DMARDS; *eg*, methotrexate) not helpful in axial disease but can be helpful in peripheral disease; anti-tumor necrosis factor (TNF) agents and secukinumab (targets interleukin [IL]-17A); helpful for both peripheral and axial joint pain

Psoriatic arthritis: arthritis occurring in conjunction with psoriasis; peak age of onset 40 yrs to 60 yrs; prevalence ~1% of general population; 15% to 20% of people with psoriasis develop PsA; axial involvement in PsA can occur at any level of spine and may skip regions of spine; extraaxial involvement can include peripheral arthritis, dactylitis, tenosynovitis, enthesitis, and, if untreated or nonresponsive to therapy, can result in arthritis mutilans; conjunctivitis and uveitis may occur; in majority of cases, psoriasis precedes joint involvement, but sometimes joint involvement precedes skin involvement by ≤2 yrs; additional cutaneous manifestations include nail pitting and onycholysis
Presentation: *2 patterns of joint involvement* — 1. oligoarticular, asymmetric lower-extremity arthritis; 2. symmetric polyarthritis at DIP, PIP, MCP, and MTP joints; in either pattern, patients may have dactylitis, SI joint involvement, asymmetric spondylitis with skip lesions
Diagnosis:
Cl**AS**sification criteria for **P**soriatic **AR**thritis (CASPAR criteria): patient must have inflammatory

articular disease as well as 3 of 5 following criteria: 1. personal or family history of psoriasis; 2. psoriatic nail dystrophy; 3. negative rheumatoid factor (RF); 4. dactylitis; 5. Radiographic evidence of juxtaarticular new bone formation

Other: negative RF part of CASPAR criteria, but small percentage of patients have positive RF; *physical exam* — spine tenderness, SI joint tenderness, peripheral joint arthritis, dactylitis, enthesitis, psoriasis, nail dystrophy, or onycholysis; *laboratory*- CBC, comprehensive metabolic panel, HLA-B27, ESR, C-reactive protein, RF, and anti-cyclic citrullinated peptide (CCP) blood test; if expecting to use biologic DMARD, test for tuberculosis (TB) and hepatitis; *imaging* — x-ray of affected joints if peripheral arthritis; x-ray of SI joints or spine if axial involvement

Management: collaboration between rheumatologist and dermatologist; *conservative management* — exercise, localized corticosteroid injections into joints or skin; *medications*- topical creams for skin disease, NSAIDs for joint pain, conventional DMARDs for peripheral arthritis, biologic DMARDs (including anti-TNF agents, ustekinumab, secukinumab, tofacitinib, and apremilast)

Inflammatory bowel disease–related arthritis: associated with IBD; involve axial and peripheral skeleton; 20% to 30% of individuals with IBD will develop IBD-related arthritis; axial involvement in IBD-related arthritis does not parallel bowel disease activity; SI joint involvement often present in axial disease of IBD arthritis, frequently asymmetric; *peripheral involvement has 3 different patterns* — 1. monoarticular large-joint involvement of lower extremity, parallels IBD activity; 2. polyarticular small-joint arthritis in upper extremities; does not parallel IBD; possibly enthesitis or dactylitis; 3. skin disease that manifests as pyoderma gangrenosum or erythema nodosum, uveitis (insidious or chronic, usually anterior and bilateral), episcleritis or conjunctivitis; increased risk of thromboembolism in patients with IBD; also increased risk of nephrolithiasis and renal disease

Diagnosis: based on history of IBD (*eg*, Crohn disease or ulcerative colitis) and presence of axial or peripheral arthritis meeting above patterns; *imaging* — to demonstrate changes related to IBD arthritis; x-rays of involved joints important

Management: glucocorticoids; biologic DMARDs may help control both IBD and arthritis

Reactive arthritis: noninfectious inflammatory arthritis; occurs after GI or genitourinary (GU) infection; autoimmune process, not infectious; usually 3 wks to 6 wks after infection, but latency can be anywhere from 2 wks to 6 mos after infection; 50% of cases resolve within 6 mos; 20% become chronic; once patient has episode reactive arthritis, increased risk for repeated episodes thereafter; associated GI pathogens include *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli*, and *C difficile*; associated GU pathogens include *Chlamydia* and *Ureaplasma urealyticum*

Diagnosis: based upon clinical presentation and history of antecedent infection; other manifestations include skin findings (*eg*, keratoderma blenorrhagicum, circinate balanitis), enthesitis, and asymmetric large-joint oligoarthritis; nonerosive arthritis, so x-rays not helpful(but can distinguish reactive arthritis from another suspected process)

Treatment: conservative; localized glucocorticoid injections, NSAIDs; rarely, conventional or biologic DMARDs

Gout: painful joint inflammation caused by monosodium urate crystals; prevalence 4% in US; risk factors include genetic factors, age, chronic kidney disease; men and postmenopausal women have higher risk; comorbidities include diabetes, kidney disease, obesity, vascular disease, and dyslipidemia

Pathophysiology: uric acid end product of purine metabolism in humans; other animals (*eg*, birds) have uricase (enzyme that breaks down uric acids), humans do not; xanthine oxidase breaks down products of purine metabolism into uric acid; uric acid can accumulate; monosodium urate crystals form when uric acid concentration >6.8 mg/dL; uric acid cleared from kidney via glomerular filtration, secretion, and resorption; *causes of elevated uric acid (hyperuricemia)* — primary renal uric acid underexcretion, chronic kidney disease, uric acid overproduction resulting from defect in purine metabolism, conditions with increased cell turnover (leading to increased purines), drug-induced hyperuricemia, and diet-induced hyperuricemia; *drugs that commonly cause hyperuricemia* — thiazide diuretics, loop diuretics, low-dose salicylates, ethambutol, pyrazinamide, lead; *dietary factors that can cause hyperuricemia* — increased consumption of meat, shellfish, alcohol, high-fructose–sweetened beverages and foods; dehydration increases serum uric acid; once uric acid at level where crystals can form, monosodium uric crystals phagocytosed by macrophages, initiating inflammatory cascade 3. types of clinical presentations: *acute gouty arthritis* — red, swollen, tender joint; quick onset (occurs over 12-24 hrs); majority of first attacks monoarticular, beginning at night and in lower extremity; low-grade fever, peripheral leukocytosis, elevated inflammatory markers; associated inflammatory changes in surrounding soft tissues that may mimic cellulitis; uric acid may be normal at time of attack, probably from increased uric acid excretion caused by circulating cytokines; *intercritical gout* — period between gout attacks; tophi may be forming, but no acutely red, swollen, or tender joint; *chronic recurrent tophaceous gout* — also called pseudorheumatoid arthritis; frequent attacks so close in timing that seem contiguous or chronic arthritis with synovitis-like presentation; possible to confuse chronic recurrent gout with rheumatoid arthritis

Tophus: stone-like deposit of monosodium urate surrounded by inflammatory fibrous rind outside of joint; hallmark of gout; typical on tendons (*eg*, Achilles tendon), tips of ears

Diagnosis: consider gout with acute monoarticular or polyarticular inflammation; *laboratory* — serum urate levels may be elevated in acute attack, but may also be normal, so not used as diagnostic criterion (poor negative and positive predictive value); joint aspiration gold standard for diagnosis; inflammatory synovial fluid with elevated WBC count, neutrophilic predominance; negative culture; polarized microscopy analysis of joint

fluid shows needle-shaped, negatively birefringent crystals; *imaging* — not useful in diagnosing acute gout, but can help rule out other conditions; monitors for gout-related changes in chronic gout; gouty erosions seen on x-ray appear as punched-out lesions or "rat-bite" lesions, characterized by overhanging edges

Differential diagnosis: infectious arthritis, acute pseudogout, basic calcium phosphate deposition, inflammatory arthritis (RA, PsA); joint aspiration gold standard for differential diagnosis

Management: *acute (gout flare) management* — colchicine, NSAIDs, oral or intraarticular steroids; colchicine first-line therapy if patient seeks medical attention within first 36 hrs of flare (dosed at 1.2 mg at time 0, 0.6 mg at time 1 hr, 0.6 mg daily thereafter; dosage based on renal function); *chronic management* — eliminate or limit foods and beverages that increase risk of gout (*eg*, alcohol, meat, shellfish, foods and beverages containing high-fructose sweeteners); urate-lowering therapy for patients with ≥2 gout flares in 1-yr period, or 1 gout flare in 1-year period in setting of chronic kidney disease Stage 2 or worse, kidney stones; patients with gouty erosions on x-ray or tophi should be offered urate-lowering treatment; target uric acid ≤6 mg/dL, ≤5 mg/dL if tophi present; *medications that lower uric acid* — xanthine oxidase inhibitors, allopurinol and febuxosat; probenecid, uricosuric agent, blocks renal uric acid resorption; increases risk of kidney stones, so not helpful in patients with chronic kidney disease; pegloticase, uricase that can be given intravenously (IV); high rate of allergic reactions; in patient with hyperuricemia treated with urate-lowering therapy, flare prophylaxis with colchicine, steroids, or NSAIDs while lowering uric acid until goal reached

Pseudogout (calcium pyrophosphate deposition disease [CPDD]): mostly idiopathic, increases with age, more common in women; risk factors include age, prior joint trauma, familial chondrocalcinosis and metabolic disorders, endocrine disorders; such disorders include hemochromatosis, hyperparathyroidism, gout, hypomagnesemia, hypophosphatasia, X-linked hypophosphatemic rickets, familial hypocalciuric hypercalcemia, acromegaly, Wilson disease, bisphosphonate use, and ???

Pathophysiology: excessive calcium or excessive calcium pyrophosphate; unclear mechanism

Presentation: acutely red, swollen, tender joint

Diagnosis: clinical presentation and joint aspiration; aspiration shows inflammatory joint fluid; crystal analysis shows rhomboid crystals with positive birefringence; x-ray may show chondrocalcinosis (cartilage calcification) in CPDD

Management: in acute CPDD, joint aspiration injection alleviates pain and relieves acute flare; *medications* — NSAIDs, colchicine, or glucocorticoids; if >3 attacks per yr, consider prophylaxis with colchicine, NSAIDs, or low-dose glucocorticoids

Infectious (septic) arthritis: bacterial, fungal, viral, or mycobacterial infection within joint; usually results from hematogenous spread, direct inoculation of joint, or contiguous spread; risk factors include age >80 yrs or <5 yrs, alcoholism, skin breakdown, end-stage renal disease, diabetes, history of instrumentation within region, injection drug use, low socioeconomic status, immunosuppression, sickle cell disease, and underlying malignancy; immunosuppressed patients or those who travel to or live in area where specific fungus endemic have increased risk of fungal septic arthritis

Presentation: warm, red, painful joint, decreased range of motion; bacterial infections develop over few days, while viral and fungal infections have more insidious onset; ~80% of septic arthritis cases monoarticular

Pathophysiology: *gram-positive organisms* — most common causes in adults; *Staphylococcus aureus* most common cause; toxin and local inflammatory response cause damage to joints; joint damage may develop within 48 hrs of development of septic arthritis; *gram-negative organisms* — nongonococcal gram-negative organisms such as *E coli*, *Pseudomonas*, and *Salmonella* (more prevalent in patients with sickle cell disease); 3% of patients with systemic gonorrhea develop disseminated gonococcal arthritis; *2 types of gonococcal arthritis* — 1. purulent arthritis; no rash; no bacteremia; usually monoarticular or oligoarticular; positive cultures; localized septic arthritis, direct infection of joint; knee most common but seen in wrists, ankles, and elbow; 2. disseminated gonococcal disease with arthritis; does not involve direct infection of joint; bacteremia but negative synovial culture (synovial WBC <25,000); arthritis dermatitis, vesiculopustular or hemorrhagic macular lesions; polyarthralgia, tenosynovitis, fever and chills

Diagnosis: *laboratory* — joint aspiration for culture, cell count, gram stain, and crystal analysis; cultures 80% sensitive to identify bacterial cause; WBC count usually >50,000, with neutrophil predominance; important to aspirate joint before starting antibiotic treatment; if gonococcal arthritis suspected, get GU and pharyngeal culture, both traditional culture media and chocolate agar; *imaging* — x-ray to identify early osteomyelitis or erosions caused by aggressive septic arthritis

Lyme arthritis: infection with *Borrelia* species; 3 phases of Lyme disease

Presentation: arthralgia can be seen in early localized or early disseminated Lyme disease; arthritis seen in late Lyme disease, causes frank inflammation of joints, large effusions, and usually monoarticular or oligoarticular pattern with stiffness; prominent stiffness, little pain

Diagnosis: serologic diagnosis with positive ELISA test and Western blot test; joint aspiration shows moderately elevated WBC count (20,000-25,000) with high percentage of neutrophils and negative cultures; *Borrelia burgdorferi* DNA can be tested on synovial fluid

Mycobacterial arthritis: *TB* — 20% of TB infections extrapulmonary; joint or bone involvement seen in 2% of TB infections

Presentation: joint involvement in initial infection or reactivation of latent TB; chronic, indolent infection; patient may or may not have other signs of TB; usually monoarticular; synovial fluid may be bland

Diagnosis: synovial fluid, specific culture for acid-fast bacilli; if strong suspicion for mycobacterial arthritis, synovial biopsy superior to acid-fast bacilli culture on synovial fluid (synovial fluid acid-fast bacilli cultures have high false-negative rate)

Mycobacteria marinum — fresh- and saltwater organism that enters through breaks in the skin; presents with red or purple plaque, nodules, abscesses under skin

Fungal arthritis: more common in immunosuppressed persons and in endemic areas; common causative fungi include *Coccidioides*, *Sporothrix*, *Cryptococcus*, *Blastomyces*, and *Candida*; fungal arthritis usually monoarticular; diagnosis by fungal culture and/or synovial biopsy

Viral arthritis: *hepatitis B* — can cause symmetric polyarthritis in prodrome stage of disease; associated with rash; can be transient or persistent; *hepatitis C* — causes arthralgia or arthritis; can be oligoarticular or polyarticular; *parvovirus* — symmetric swelling and stiffness of small joints of hands, feet, wrists, and knees; consider in adult population; can last for wks or mos; usually positive parvovirus IgM; can be managed with NSAIDs and steroids; consider parvovirus in patient with abrupt, symmetric inflammatory arthritis; *rubella* — rash, fever, lymphadenopathy, polyarthritis; positive IgM serology at time of arthritis; resolves in 2 wks; *chikungunya and Zika virus*- self-limited; supportive care required

Diagnosis: travel history; serology to help guide and diagnose

Prosthetic joint infections: rare complication of joint replacement; occurs in 2% of patients who have had joint replacement; most common, *Staphylococcus* within 2 yrs of surgery; risks include superficial skin infection or surgical-site infection, immunosuppression, and chronic illness; *3 types of prosthetic joint infections*- 1. early-onset (within 3 mos after surgery); joint swelling, erythema, wound drainage, fever; 2. delayed-onset (within 3-12 mos after surgery); insidious and prolonged joint pain, may be confused with prosthetic failure; 3. late-onset (12 mos after surgery); acute pain and swelling

Management: aspiration of joint, prompt orthopedic evaluation; if suspicion of gram-positive cocci, administer vancomycin, linezolid, clindamycin, or daptomycin if methicillin-resistant *S aureus* (MRSA) suspected; but if methicillin-susceptible *S aureus* (MSSA) suspected, oxacillin, nafcillin or cephazolin; for gram-negative bacilli, third-generation cephalosporin or fluoroquinolone; *Pseudomonas* requires treatment with ceftazidime, aminoglycoside, carbapenem, piperacillin, cefepime, tazobactam, or fluoroquinolone; *Neisseria gonorrhoeae* requires treatment with IV ceftriaxone or fluoroquinolone; if gram stain unclear or unavailable, broad-spectrum treatment with vancomycin plus third-generation cephalosporin recommended; for suspected Lyme disease, oral doxycycline or amoxicillin; *Mycobacterium tuberculosis* treated with anti-TB therapy(isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin); for fungal infection, amphotericin or azoles; regardless of antibiotic, must drain purulent fluid from joint with bacterial infection

Suggested Reading

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Rheumatoid Arthritis and Systemic Lupus Erythematosus

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Rheumatoid Arthritis

Overview: rheumatoid arthritis (RA), chronic systemic autoimmune disease; involves primarily joints, causing inflammatory polyarthritis; most common inflammatory joint disease; affects 1% to 2% of population; 2 to 3 times more frequent in women; onset can be at any age, most frequently between ages 30 yrs and 50 yrs; etiology unknown; *complex pathogenesis*- involves combination of genetic, environmental, and hormonal factors; many genes have been studied; most significant genetic risk factors for RA appear to be variations in human leukocyte antigen (HLA) genes, especially HLA-DRB1; environmental triggers may include infectious agents, cigarette smoking, and certain occupational exposures; since 70% of people affected women, female hormones likely play role in pathogenesis; immunologic abnormalities include immune complex formation, autoantibodies, and CD4-positive lymphocytes and macrophage infiltration of synovial tissue, resulting in severe inflammation; over time, chronicity leads to synovial proliferation, which releases inflammatory mediators resulting in destruction of cartilage and bone

Diagnosis: clinical manifestations most important in diagnosis; RA should be suspected in patients with symmetric inflammatory polyarthritis of duration of ≥6 wks, especially if hands affected; onset of disease usually in stages, starting with symptoms of joint pain, swelling, and stiffness; systemic symptoms (fatigue, malaise, generalized weakness, low-grade fever, unintentional weight loss) also common; joint symptoms typically symmetric, affecting multiple small and large joints; polyarthritis hallmark of disease, but RA can start as mono or oligoarticular

Signs and symptoms: joint stiffness prolonged, lasting ≥1 hr, usually after rising in morning or following periods of prolonged inactivity throughout day; joint stiffness improves with physical activity; on physical exam, joints usually very tender, swollen, and warm; erythema not common; any joint can be affected; most common joints affected include wrists and metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints; distal interphalangeal joints and thoracic and lumbar spine rarely affected; note that cervical spine commonly affected and can result in serious complications (*eg*, atlantoaxial instability, subaxial subluxation); therefore, important to evaluate cervical spine of all patients with RA undergoing general anesthesia

Autoantibodies: clinical diagnosis may be supported by presence of autoantibodies (*eg*, rheumatoid factor [RF], anti–cyclic citrullinated peptide [anti-CCP]); however, not diagnostic; absence does not exclude diagnosis of RA; these antibodies may be negative in 20% to 30% of patients with RA; anti-CCP has higher specificity for RA (≤90%); both RF and anti-CCP predict worse disease prognosis

Diagnostic tests: laboratory studies nonspecific; findings include normocytic normochromic anemia, mild to moderate leukocytosis and thrombocytosis, elevation of inflammation markers (*eg*, sedimentation rate and C-reactive protein); mild polyclonal hypergammaglobulinemia common; X-rays of hands and feet may be normal early in course of disease; when X-rays abnormal, usually show soft tissue swelling; in chronic disease, bone erosions may be seen on X-ray in advanced RA; MRI more sensitive, detects early signs of inflammation and damage when X-ray may still be normal

Differential diagnosis: includes all diseases that can be associated with polyarthritis, *eg*, systemic lupus erythematosus (SLE), crystal-induced arthritis (*eg*, gout, pseudogout), sarcoidosis, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, hepatitis C, and osteoarthritis; arthrocentesis of swollen joint for synovial fluid analysis and cultures frequently necessary for diagnosis

Extraarticular manifestations: although rheumatoid arthritis affects primarily joints, extraarticular manifestations may occur in ≤40% of patients; often serious conditions that require aggressive treatment; significant decline of prevalence of extraarticular manifestations in last 10 yrs, because of development of new medications and early treatment; Sjögren syndrome secondary to RA one of most common extraarticular manifestations; rheumatoid nodules present ≤30% of patients, more commonly in subcutaneous tissue but also in many other locations, including lungs; other extraarticular manifestations include pleural or pericardial effusions, pericarditis, myocarditis, secondary Sjögren syndrome, episcleritis and Felty syndrome (RA with neutropenia and splenomegaly); vasculitis of small vessels rarely seen but can cause severe skin ulcers and neuropathy with devastating disability; atherosclerosis most common cardiovascular (CV) manifestation in RA and main cause of death; extraarticular RA more common in patients with positive RF or anti-CCP, more severe and erosive joint disease

Treatment of RA: combination of multiple medications, physical therapy, and surgery; joint deformity end result of continuous inflammation, causing loss of joint function, tendon rupture, cysts, and significant disability or morbidity; therefore, treatment important early in disease; lifestyle modifications include smoking cessation, healthy nutrition, and regular physical activity; joint rest rarely beneficial; joint surgeries may be necessary in patients with advanced chronic disease and severe joint deformities; joint replacements most common joint surgeries performed, but aggressive early treatment with disease-modifying agents (disease-modifying antirheumatic drugs; DMARDs) key to therapy

DMARDs: medications from different classes often used in combination; *methotrexate (MTX)* — initial treatment of choice; should always be considered unless contraindication to its use; if well tolerated, MTX dose can be increased at 4- to 5-wk intervals, to maximum of 25 mg once per wk; if response to MTX incomplete or inadequate, other medications can be added or therapy can be switched; combination therapy options include sulfasalazine, hydroxychloroquine, and leflunomide; leflunomide can also be used as monotherapy; *biologic agents* — biologic agents of different classes commonly added to MTX but not combined to each other because of potential toxicity; tumor necrosis factor (TNF)-alpha inhibitors include infliximab, etanercept, adalimumab, golimumab, and certolizumab; TNF-alpha inhibitors associated with reduction of inflammation and reduction of joint damage progression; TNF-alpha inhibitors usually first option of medications used in combination with MTX; if treatment with TNF-alpha inhibitors fails, other biologic agents commonly used; these include belatacept (selective T-cell costimulation blocker), rituximab (anti-CD20 antibody that depletes B cells), anakinra (interleukin [IL]-1 receptor antagonist), tocilizumab (IL-6 blocker), and tofacitinib (Janus kinase inhibitor given orally); serious infections including reactivated tuberculosis (TB) main risk associated with these agents

Summary: early diagnosis and early institution of disease-modifying treatment may result in preservation of joint function and increased life expectancy in patients with RA

Systemic Lupus Erythematosus

Overview: systemic lupus erythematosus (SLE), inflammatory multisystem autoimmune disease; prototype of autoimmune disease, associated with presence of pathogenic autoantibodies; unknown etiology; estimated incidence 1 in 100,000 to 25 per 100,000 in US; women of childbearing age (aged 15-40 yrs) at greatest risk; only 10% of patients male; SLE 2 to 4 times more frequent and more severe among non-white populations (eg, African Americans, Asians, Hispanics); tends to be more severe in men, in pediatric patients, and in late-onset lupus

Pathogenesis: complex; involves genetic, hormonal, and environmental factors; global loss of self-tolerance with failure to clear apoptotic cell debris; multiple abnormalities of innate adaptive immune system with activation of autoreactive B and T cells, leading to autoantibody secretion, circulating immune complexes, and immunoglobulin and complement activation, resulting in tissue injury with early atherosclerosis and complement deficiencies; association of HLA genes in SLE not uniform; multiple genes likely responsible and associated with different disease patterns; some cases of lupus have been associated with rare but highly penetrant mutation, homozygous deficiency of complement C1q, C2, or C4; in majority of cases, genetic susceptibility probably determined by relatively common variants

Signs and symptoms: heterogeneous; can affect every organ system in body at different times; clinical course typically characterized by periods of exacerbations and remissions; manifestations range from very mild to severe or life threatening; most frequent manifestations nonspecific and include constitutional symptoms such as fatigue, malaise, fever, and weight loss; myalgias, arthralgias, and mucocutaneous lesions also common; *skin* — frequently affected in SLE; skin manifestations include malar rash, annular polycyclic papulosquamous rash seen in subacute cutaneous lupus, and discoid lesions of chronic lupus; nonspecific lesions common and include urticaria, erythema nodosum, livedo reticularis, alopecia, oronasal lesions, Raynaud phenomenon, and, rarely, vasculitis; *musculoskeletal* — >50% of patients commonly present with symptoms of arthralgias or arthritis; arthritis typically not erosive or destructive; may result in clinical reversible deformity called Jaccoud arthropathy (result of subluxations, not joint disruption); avascular necrosis can be complication of lupus or result from steroid treatment; myositis frequently causes pain and weakness; *other organs and systems* — serositis can result in pleurisy, pericarditis, or peritonitis; pleural and pericardial disease usually asymptomatic or very mild, more commonly found in autopsy studies; pleural effusions tend to be small and bilateral; when large, infections need to be excluded (exudate more commonly seen); peritonitis can be severe and may present as severe acute abdominal pain, anorexia, nausea, vomiting, and can mimic bowel perforation, acute pancreatitis, and infectious peritonitis; pulmonary involvement usually mild but frequent; pleurisy most common symptom, with or without pleural effusions; less-common presentations include acute pneumonitis (may be clinically similar to infection), chronic interstitial disease (rarely results in fibrosis), pulmonary hemorrhage (rare but associated with high mortality), and pulmonary hypertension and shrinking lung syndrome (both rare but serious complications)

Case study 1: African American female aged 38 yrs with 10-year history of SLE; serositis, rash, glomerulonephritis, seizures, and Raynaud syndrome; positive antinuclear antibodies (ANAs) and anti–double-stranded DNA; low C3 and C4; taking low-dose prednisone continuously for last 5 years because of recurrent episodes of rash, joint pain, and oral ulcers; presents to the emergency department (ED) with chest pain and dyspnea; blood pressure (BP) 170/98 mm Hg; heart rate 104 bpm; on exam, lungs clear, no pleural or pericardial rubs

Discussion of case study: most frequent cause of mortality in this patient not pulmonary hypertension, pleural effusion, Libman-Sacks endocarditis, or myocarditis; most frequent cause of mortality myocardial infarction; all layers of heart can be affected in SLE and may result in pericarditis, myocarditis, or endocarditis; however, early accelerated atherosclerosis most common cardiac complication in SLE; multiple studies emphasized increased risk for premature atherosclerosis and CV

disease in patients with SLE; beyond initial phase of disease, CV death main cause of mortality; many patients with SLE have subclinical atherosclerosis early in disease course; risk of coronary artery disease at any level of traditional CV risk factors higher in lupus than in general population; also increased incidence of carotid plaques, intimal-medial thickness and endothelial dysfunction; risk of CV disease higher with longer duration of SLE; in patients with vascular event, mortality twice as high in SLE than in other patient groups; risk factors associated with CV disease in SLE include endothelial dysfunction, inflammatory process itself, anticardiolipin antibodies, and impaired renal function

Other signs and symptoms:

Neuropsychiatric (rare in adults): seizures, stroke, aseptic meningitis, transverse myelitis, cranial neuropathy, peripheral neuropathy, organic brain syndrome, psychosis, and neurocognitive dysfunction manifestations of neuropsychiatric disease; rare but potentially serious; headaches common in SLE

Hematologic abnormalities (common): anemia may have different etiologies including Coombs-positive or -negative hemolytic anemia; leukopenia common, not always associated with active disease, does not always require treatment; thrombocytopenia may be severe, refractory, and associated with active disease or isolated feature independent of disease activity; can also be secondary to antiphospholipid syndrome or TTP

Case study 2: woman aged 23 yrs presents with facial and body rash, joint pain, and recurrent oral ulcers; 2 recent episodes of joint pain and was seen in the ED; treated for pain; positive ANA; since second episode, she continued to have daily joint pain; on exam, she has rash; no joint swelling; no oral or nasal lesions

Questions: *what would be most important initial test in diagnostic evaluation of this patient*? — anti–double-stranded DNA, complete blood cell count (CBC) with platelets, antiphospholipid antibodies, or urine sediment and creatinine

Discussion of case study 2: all tests important, but urine sediment and creatinine most important tests; renal disease present in ≤60% of patients and usually clinically silent; should be suspected in presence of microscopic hematuria, cellular casts, and proteinuria >0.5 g in a 24-hor period; World Health Organization (WHO) classification of lupus glomerulonephritis based on light, immunofluorescence, and electron microscopy results; *divides lupus nephritis into 5 different classes* — Class 1, minimal mesangial lupus nephritis; Class 2, mesangial proliferative lupus nephritis; Class 3, focal lupus nephritis; Class 4: diffuse lupus nephritis; Class 5: membranous nephritis; role and timing of renal biopsy not always clear, can be controversial; initial biopsy usually done to guide treatment decision and predict prognosis and outcome; repeat biopsies not clearly indicated; may be needed when change in treatment required, because histology may change over time, and to determine whether disease flare vs end-stage renal disease

Differential diagnosis: extensive; includes antiphospholipid syndrome, fibromyalgia, hepatitis C, sarcoidosis, infective endocarditis, Lyme disease, lymphoma, mixed connective tissue disease, preeclampsia, rheumatic fever, RA, scleroderma, serum sickness, thrombotic thrombocytopenic purpura, and undifferentiated connective tissue disease

Diagnosis: based mainly on clinical presentation, supported by laboratory testing; *diagnostic challenges* — 1. possibly only few manifestations at onset and disease may evolve slowly over long period of time; 2. disease may be present with intermittent signs and symptoms and long periods of exacerbations and remissions; 3. many other multisystem diseases may mimic SLE, making it difficult to establish diagnosis with certainty; *American College of Rheumatology (ACR) criteria* — ACR criteria for classification of SLE (revised in 1997) establish that any combination of ≥4 of 11 criteria (well documented at any time during patient's history) makes it likely that patient has SLE (specificity 95%, sensitivity 75%); however, these criteria not developed for diagnosis in clinic, but to guarantee patient comparability in research trials; patients with early SLE may have only few symptoms and therefore not fulfill criteria; spectrum of clinical manifestations in SLE much greater than outlined by ACR criteria; however, criteria can be used for reminders of common features associated with SLE

Laboratory tests: laboratory abnormalities florid in SLE; ANA positive >98% of patients; however, ANA nonspecific, also present in healthy controls, and in primary Sjögren syndrome, scleroderma, juvenile RA, and RA, among others; anti–double-stranded DNA more specific for SLE, (specificity >90%); in some patients, titer may correlate with disease activity; hypocomplementemia common in SLE; low C3 and C4 may be associated with disease flares in some patients, especially in those with glomerulonephritis

Examples of autoantibodies and their clinical association and frequency: the anti–double-stranded DNA present in only ~70% of patients but highly associated with those with nephritis; anti-Smith antibody, although very specific for lupus, has low frequency (30%); the anti-SSA more associated with subacute cutaneous lupus and anticardiolipin with arteriovenous thrombosis, recurrent fetal loss, and thrombocytopenia

Drug-induced lupus syndrome: very similar to idiopathic SLE, but usually much milder disease; renal and central nervous system (CNS) disease rare; common features of drug-induced lupus include constitutional symptoms, arthralgias, rash, pleural pulmonary disease; ANA present in ~99% of patients; anti–double-stranded DNA rarely seen; histone antibodies present in 95% of cases (note that antihistone antibody not exclusive to drug-induced lupus, also seen in idiopathic SLE); drug-induced lupus usually resolves after discontinuation of drug and rarely requires therapy

Treatment of SLE: determined by multiple factors including individual patient factors; presence or absence of disease activity; the disease extension (organ systems involved); disease severity; possibly ethnicity; prognostic factors (eg, presence of glomerulonephritis)

Treatment of mild disease: patients with constitutional symptoms, musculoskeletal disease, skin involvement, serositis; treatment usually includes nonsteroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, and low-dose oral corticosteroids; calcium channel blockers to treat Raynaud syndrome

Treatment of severe disease: patients with cardiac, renal, and CNS involvement; requires high-dose corticosteroids in combination with second immunosuppressive agent

(*eg*, cyclophosphamide, azathioprine, mycophenolate mofetil, or rituximab)

Treatment of lupus nephritis: clinical evidence of glomerulonephritis in ~30% of patients at diagnosis and ≤60% of first 10 yrs of disease; higher in African American and Hispanic persons; high mortality rate; *treatment guided by WHO classification* — Class 1 and Class 2 may not require immunosuppressive treatment, but close monitoring necessary; Class 3 and Class 4 require aggressive therapy with glucocorticoids in combination with second immunosuppressive agent (*eg*, mycophenolate mofetil or intravenous (IV) cyclophosphamide can be used along with glucocorticoids as initial therapy); good results for induction therapy with mycophenolate mofetil, which can be used later as maintenance therapy at lower doses for 3 yrs or longer; mycophenolate mofetil has similar efficacy in all studied races; pure membranous (Class 5) with nephrotic range proteinuria should be treated with prednisone plus mycophenolate mofetil at 2 g to 3 g daily (normally given divided into 2 doses); mycophenolate mofetil superior to azathioprine in preventing relapses of lupus nephritis; IV methylprednisolone 1000 mg/day for 3 days commonly used in severe disease

Belimumab: fully human monoclonal antibody against B-lymphocyte stimulator; used in mild to moderate SLE; only FDA-approved drug in SLE; however, renal and CNS disease excluded from studies, therefore not indications for treatment with belimumab; patients with stable disease receiving standard-of-care treatment may be candidates for belimumab; improvement in various clinical measurements of disease activity seen with belimumab; patients also able to reduce steroid dosages with belimumab

Summary: significantly improved survival in persons with SLE in last 10 yrs, possibly because of early diagnosis, increased use of dialysis in renal transplant, and use of more potent immunosuppressive agents early in disease course; mortality rate still 3 to 5 times greater than in general population; however, improvement in survival over time demonstrated when examining all causes of death together, but not when examining those deaths from CV disease; monitoring disease activity over time, as well as preventive care, in SLE include monitoring clinical symptoms with laboratory tests (*eg*, CBC, urine sediment, and renal function throughout lifetime); following autoantibody positivity or titers usually not useful; ANA should not be monitored for assessment of disease activity and should not be used in treatment decisions; anti–double-stranded DNA may be useful in certain patients with nephritis; monitoring bone density for early detection and treatment of steroid-induced osteoporosis important; prophylactic immunization should be given prior to starting immunosuppression, if possible; aggressive control of traditional risk factors of atherosclerosis such as hypertension, hyperlipidemia, and diabetes should be started early in patients with SLE

Suggested Reading

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Vasculitis, Systemic Sclerosis, Inflammatory Myopathies, and Fibromyalgia

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Vasculitis

Systemic vasculitis: divided into large-, medium-, and small-vessel vasculitis; *large-vessel vasculitis* includes giant cell arteritis, polymyalgia rheumatica (PMR), and Takayasu arteritis; *medium-vessel vasculitis* includes polyarteritis nodosa (PAN), primary angiitis of the central nervous system (CNS), and Kawasaki disease; *small-vessel vasculitis* includes antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis and immune complex–mediated vasculitis

Giant cell arteritis: result of cytokines from activated dendritic cells in adventitia, which recruit CD4+ helper T cells, with Th1 and Th17 cells producing interferon-gamma and interleukin (IL)-6 and IL-17, respectively; recruited monocytes differentiate into giant cells with reduction of blood vessel patency or weakening of the vessel wall, with aneurysm formation; prominently in persons aged >50 yrs

Presentation: shoulder and hip girdle pain, visual disturbances (*eg*, diplopia), headache, jaw claudication, neck pain, scalp tenderness, impaired circulation, constitutional symptoms (fatigue, malaise, fever); transient ischemic attacks (TIAs) may be noted; no objective muscle weakness

Evaluation: erythrocyte sedimentation rate (ESR) may be normal but normal ESR does not rule out diagnosis; complete blood count (CBC), liver enzymes, and complete physical examination, including visual fields, should be performed; consider ophthalmology consult; temporal artery biopsy to confirm diagnosis; ultrasound, angiography — both magnetic resonance imaging (MRI) and positive emission tomography (PET scan) used to assess; tuberculosis (TB) tests indicated if steroids considered

Management: high-dose steroids (*eg*, prednisone 40-60 mg/d); perform temporal artery biopsy within 1 week; if any visual or neurologic symptoms, treat with prednisone 80 to 100 mg or intravenous (IV) methylprednisolone; continue medication for 4 wks or until symptoms and laboratory abnormalities resolve, then reduce by 10% every 1 to 2 wks; low-dose aspirin to reduce cranial ischemic complications; proton pump inhibitor (PPI) for gastrointestinal (GI) protection; bisphosphonates, calcitonin, vitamin D for bone protection while on steroids; tocilizumab (IL-6 receptor inhibitor) can be used; cyclosporine, azathioprine, or methotrexate also useful as steroid-sparing agents

Complications: vision loss, myocardial infarction (MI), stroke, dissecting aneurysm, aortic regurgitation; 50% of patients experience sudden death from aortic aneurysms; 50% of patients have concurrent PMR;

Prognosis: full recovery with prompt, adequate intervention; blindness, MI, stroke, or dissecting aneurysm with death if intervention delayed; if ESR does not normalize within 1 week with high-dose steroids, rheumatologic evaluation recommended

Polymyalgia rheumatica: unknown etiology, associated with IL-6 elevation; usually seen in individuals aged >50 yrs

Presentation: shoulder and hip girdle pain, stiffness, difficulty raising arms over head (subjectively); no objective muscle weakness; ESR usually >40 mm/hr; morning stiffness, fever, weight loss, and malaise may also be noted; synovitis controversial in differential from rheumatoid arthritis (RA)

Evaluation: ESR, rheumatoid factor (RF), cyclic citrullinated peptide (CCP) antibodies, C-reactive protein (CRP), CBC, creatinine, glucose, creatine phosphokinase (CPK), liver function tests, aldolase, calcium electrophoresis, thyroid function such as thyroid-stimulating hormone (TSH), vitamin D

Management: rapid response to prednisone, usually 10 mg/d, tapering at monthly intervals by 10%; nonsteroidal anti-inflammatory drugs (NSAIDs)not used because they reduce ESR but not risk of ocular compromise; 15% of patients have associated arteritis; amyloidosis occasionally noted

Prognosis: excellent with prompt, adequate treatment; if ESR does not normalize on prednisone 10 mg/d, consider rheumatology consult because other disorders can mimic PMR

Takayasu arteritis: inflammation of large to medium-sized vessels, which can reduce vascular lumen or cause aneurysms

Presentation: constitutional symptoms (fever, headache, malaise, arthralgias, weight loss), bruits (especially of coronary artery), blood pressure (BP) differential of extremities, claudication, vascular tenderness, hypertension, renal artery stenosis, aortic regurgitation, Raynaud phenomenon, pericarditis, congestive heart failure (HF), MI, ischemia, dilated cardiomyopathy, myocarditis, visual disturbance, TIA, stroke, seizures, subacute nodular lesions, erythema nodosum, pyoderma gangrenosum

Evaluation: physical examination essential for diagnosis; testing includes ESR, ANCA, antiendothelial antibodies, *eg*, vascular cell adhesion molecule 1 (VCAM-1); focal narrowing may be noted on computed tomography

(CT) scan, MRI angiography, ultrasound, and on 18F-fluorodeoxyglucose PET scans
Management: steroids, IL-6 inhibitors (tocilizumab), cytotoxic tumor necrosis factor (TNF) agents, and surgery
Complications: aortic aneurysm, hypotensive ischemic retinopathy, vertebrobasilar insufficiency, microaneurysms, carotid stenosis, hypertensive encephalopathy, intracranial hemorrhage, seizures, stroke, myocardial infarction, valvular heart disease, and inflammatory bowel disease
Prognosis: significant morbidity; potentially life threatening; variable activity over many yrs; 20% of patients monophasic — good prognosis; individuals with ≥2 complications have 5-yr survival of 69%, 10-yr survival rate of 36%; patients with isolated disease have 100% 5-yr survival rate, 96% 10-yr survival rate; rare disease, so should get rheumatology/cardiology consult

Polyarteritis nodosa: most common disease of medium-sized vessels affected by arteritis; involves medium and small vessels with inflammation of all 3 vessel layers, producing microaneurysms with rupture and thrombosis; often related to hepatitis B or C infection, potentially other viruses
Presentation: constitutional symptoms, diastolic hypertension, livedo reticularis, abdominal pain, pancreatitis, cholecystitis, bowel infarction, testicular or ovarian pain, renal insufficiency or failure, arthritis, myalgia, polyneuropathy, peripheral neuropathy, mononeuritis multiplex, headache, psychosis, cutaneous ulcerations, gangrene of extremities, aneurysm rupture, stroke, encephalopathy, myelopathy, heart failure, myocardial infarction, pericarditis, other associated phenomena
Evaluation: ESR, CRP, CBC, liver enzymes, renal studies, urinalysis, electrophoresis, hepatitis B and C assays, cryoglobulin assay, angiography, magnetic resonance angiography (MRA); nerve conduction studies and biopsy may be required for differential diagnosis
Management: steroids; if hepatitis B, antivirals and plasmapheresis (but never cyclophosphamide) recommended; prophylaxis for pneumocystis pneumonia recommended
Complications: pancreatitis; cholecystitis; bowel, testicular, or ovarian infarction; renal insufficiency; arthritis; myalgia; mononeuritis multiplex; cutaneous ulcerations; gangrene of extremities; aneurysm rupture , which may affect kidneys, liver, heart, pancreas, axillary and brachial arteries; stroke, encephalopathy, myelopathy, HF, myocardial infarction, pericarditis
Prognosis: untreated individuals survive wks to mos; 5-yr survival 13% — half of patients die within 3 mos; steroids reduced mortality to 50% and 20% by additional immunosuppressants; neurologic involvement carries worse prognosis, can take up to 18 mos to resolve; relapsing course — one-third of patients relapse within first 5 yrs, especially those with GI involvement; if creatinine >1.6 mg/dL, protein >1 g/d, or GI, central CNS, or cardiac involvement, mortality increases to 12%-25% with 1 complication, ~50% with ≥2 complications; consultation required for symptoms that persist despite steroid therapy

Primary angiitis of the CNS: rare disease; difficult to diagnose; characterized by inflammation of blood vessel walls with vascular occlusion and aneurysms, resulting in ischemia; generally absence of clinical, laboratory, or radiologic features
Presentation: headache, altered mental status, localized weakness, aphasia, ataxia, nonspecific visual complaints, seizure among common presenting symptoms; ~15% of patients exhibit constitutional symptoms (fever, fatigue, weight loss) — uncommon; acute or subacute encephalopathy, relapsing-remitting neurologic defects, rapidly progressive space-occupying lesions with headache and focal neurologic defects
Evaluation: cerebrospinal fluid (CSF) assessment — clonal bands may be noted (as with multiple sclerosis), CBC, ANA, RF, anti-SSA and anti-SSB tests, ANCA (both P and C varieties), cryoglobulin, complement levels; MRI, angiography, brain biopsy; ESR usually normal
Management: cyclophosphamide and steroids initially; oral prednisone should be started at high dose with reduction of 10% at weekly intervals; azathioprine may be substituted for cyclophosphamide
Complications: encephalopathy, seizure, stroke, and mental decline
Prognosis: fatal prior to introduction of steroids and immunosuppressants; 14% of patients died or had severe morbidity; rheumatologic and neurologic evaluation should be routine

Kawasaki disease: unknown etiology; rule out staphylococcal scalded skin syndrome
Presentation: fever, irritability; bilateral conjunctivitis, anterior uveitis; perianal erythema; sterile pyuria, erythema and edema of hands and feet (may impede ambulation); "strawberry tongue," lung fissures, hepatic, renal, and GI dysfunction; myocarditis, pericarditis, isolated lymphadenopathy; most important diagnostic finding — desquamation of tips of fingers and toes (also seen with scalded skin syndrome), transverse screws across fingernails and toenails (Beau lines)
Evaluation: ESR, CRP, alpha-1 antitrypsin, echocardiography
Management: aspirin, IV immunoglobulins (IVIG), steroids, and methotrexate; cyclophosphamide or TNF agent for resistant cases; antiplatelet agents or anticoagulants in patients at increased risk for thrombosis or for significant coronary involvement; ulinastatin (neutrophil elastase inhibitor) sometimes used
Complications: coronary artery aneurysm, anterior uveitis, hepatitis, renal and GI dysfunction, myocarditis, pericarditis
Prognosis: benign, self-limited disorder, although 2% of children aged <2 yrs die from cardiac involvement; consultation with rheumatologist and infectious disease specialist recommended

Small-vessel vasculitis: ANCA-associated vasculitis, granulomatosis with polyangiitis (formerly called Wegener granulomatosis), microscopic polyarteritis, Churg-Strauss syndrome; characterized by minimal immune deposits; inflammation of small vessels with necrosis, both absence of granuloma formation and generalized sparing of upper respiratory tract; unclear whether ANCA actually has role in pathophysiology
Presentation: flu-like symptoms, weight loss, hypertension, rash, hemoptysis, dyspnea, cough, chest pain, HF, GI bleeding, abdominal pain, testicular or renal compromise, arthritis, mononeuritis multiplex, seizures, ocular pain,

visual disturbance, retinal hemorrhage, scleritis, uveitis; rarely sinusitis; sometimes dermato-pulmonary-renal syndrome with leukocytoclastic vasculitis, palpable purpura, livedo reticularis, ulcerations, necrotizing nodules, digital ischemia, urticaria

Evaluation: ESR, blood urea nitrogen (BUN), creatinine, urinalysis, ANCA, testing for perinuclear antibodies related to monoperoxidase, and cytoplasmic antibodies related to proteinase 3; blood cultures; complement (normal); chest radiographs and evaluation of organ systems via CT may also be performed; for mesenteric angiitis, biopsy may be indicated

Management: IVIG or cyclophosphamide with prednisone, reduction by 10%/wk as per symptomatology; plasmapheresis and rituximab may be needed; complications

Complications: HF present in 17%, MI in 2%, pericarditis in 10%; other complications include GI bleeding, ischemia, perforations, pancreatitis, renal compromise, pulmonary fibrosis, arthritis, mononeuritis multiplex, ulcerations, necrotizing nodules

Prognosis: with treatment, complete remission in 75% of patients, 5-yr survival 75%; adverse factors: older age at onset, number of relapses, and duration of required corticosteroid therapy; consultation with immunologist, rheumatologist, and organ-specific specialists helpful

Immune complex–mediated vasculitis: artificial construct covering several disparate diseases, all immunologic, but not necessarily immune complex diseases; often type 1 and type 2, rather than type 3 (immune complex derived) immunity; includes

Cutaneous leukocytoclastic vasculitis (hypersensitivity vasculitis): treatment — discontinue causative drugs; usually self-limited; steroids usually not required

IgA vasculitis (Henoch-Schönlein or Schönlein-Henoch disease): primarily children aged <5 yrs; arthralgias usually self-limited; no treatment needed, except if glomerulonephritis; then aggressive immunosuppressive therapy recommended

Cryoglobulinemic vasculitis: 3 varieties

Type 1: monoclonal; can be related to Waldenström macroglobulinemia or myeloma; predominant findings: hyperviscosity and thrombosis

Type 2 (mixed): cryoglobulinemia; can be related to hepatitis C infection; treatment: antiviral agents and B-cell depletion

Type 3: polyclonal; often associated with chronic infection, Sjögren syndrome, systemic lupus erythematosus (SLE)

Presentation: types 2 and 3 — arthralgia, myalgia, purpura, livedo reticularis, cutaneous ulcers, ischemia; patients with severe involvement have membranoproliferative glomerulonephritis and mononeuritis multiplex; rheumatoid factor (RF) may be positive; complement C4 low; *note:* with cryoglobulinemia, blood drawn requires immediate cooling to 37 degrees before clotting for diagnosis to be made

Antiglomerular membrane disease (Goodpasture syndrome): affects antibodies of type 4 collagen in glomeruli and pulmonary capillaries; treat with steroids

Hypocomplementemic urticarial vasculitis: treat with low-dose steroids, hydroxychloroquine, dapsone, sometimes TNF

Erythema elevatum diutinum: treat with dapsone or sulfapyridine

Related to direct immune complex deposition or direct antibody effects, leading to vascular damage and compromised blood flow

Presentation: palpable purpura, skin ulceration, pulmonary hemorrhage, glomerulonephritis

Evaluation: is by biopsy

Complications: glomerulonephritis, pulmonary hemorrhage, organ failure, death; consultation to distinguish allergic angiitis from other entities and for treatment resistance recommended

Connective Tissue Diseases

Scleroderma: affects 2 million to 10 million, predominantly female (4:1); especially common in women aged 30 to 40 yrs; slightly older distribution in men; vascular spasm and excessive collagen deposition produce fibrosis, related to excess growth factor-beta, IL-4, and platelet-derived growth factor; can be induced by vibration, silica (*eg*, arc welders), organic solvents (*eg*, toluene, benzene, xylene), aliphatic hydrocarbons (*eg*, hexene), and especially vinyl chloride, epoxy resin, 5-hydroxytryptophan, serotonin, pesticides, possibly appetite suppressants (*eg*, phenylethylamine derivatives), bleomycin, carbidopa, pentazocine, cocaine, penicillamine, paclitaxel; breast cancer setting, silicone or paraffin implants have been implicated

Presentation: vasospastic disease; typically associated with Raynaud phenomenon, skin atrophy, skin thickening, sclerodactyly, digital ulcers, subcutaneous calcifications, telangiectasias, dyspnea, dysphasia, pulmonary fibrosis; may present without any skin changes (scleroderma sine scleroderma)

Evaluation: anticentromere antibodies (ACAs) present in 70% to 80% of patients; capillary microscopy will reveal dilated capillary loops, characteristic; diagnose on basis of either sclerodermatous skin changes proximal to metacarpophalangeal joints or presence of sclerodactyly, fingertip scars, or Raynaud phenomenon; presence of Raynaud phenomenon, especially with capillary thickening, makes diagnosis likely

Management: mostly through prevention: avoiding cold exposure and tobacco use; wear socks, gloves; nifedipine, IV prostaglandins, or prostaglandin analogs can be prescribed; most important to prevent associated renal disease, generally related to malignant hypertension, with captopril (angiotensin II inhibitor); high dose may be needed, even at risk of mortality — development of malignant hypertension results in mortality, typically 100% at 3 months; pulmonary involvement treated with calcium channel blocking agents (*eg*, nifedipine), prostaglandins, or prostacyclin; cyclophosphamide used with variable success; photopheresis, methotrexate, mycophenolate, tacrolimus, or thalidomide may be used; immunosuppressive stem cell transplantation has been used in severe cases; GI involvement treated with PPIs and histamine-2 (H2) blockers

Prognosis: fatal if treated not promptly; mortality rate high from renal and lung changes, including pulmonary hypertension and pulmonary fibrosis; aggressively monitor for hypertension and pulmonary involvement — pulmonologist, rheumatologist and hypertension specialist helpful

Inflammatory Myopathies

Background: complex topic; not just polymyositis and dermatomyositis — encompasses inclusion body myositis, myositis ossificans, focal myositis, giant cell myositis, necrotizing autoimmune myopathy, others;

Evaluation: history and physical exam critical to distinguish among main disorders that can produce muscle pathology and muscle symptoms; family history of muscular dystrophy important to assess, as well as consistency and time course of symptoms; *exacerbating factors:* effect of food, temperature, exercise, "second wind" phenomenon; previously identified autoimmune, endocrine, or renal diseases; drugs such as alcohol, statins, antiretroviral agents, colchicine, vincristine, hydroxychloroquine, D-penicillamine, hydralazine, angiotensin-converting enzyme (ACE) inhibitors, procainamide, phenytoin, ketoconazole and other azole antifungal agents; important to elicit travel history; prevalence 0.5 to 8 cases per million; individuals usually aged >20 yrs, but can occur in childhood; Blacks more commonly affected (4:1), women (2:1); contrasts with inclusion body myositis, in which individuals usually aged >50 yrs

Presentation: *inclusion body myositis:* immune complex disorder; weight loss, arthralgias, fever, malaise, proximal muscle weakness, myoglobinuria, sensory defects; muscular symptoms include insidious onset of symmetrical muscle weakness, intramuscular calcification, specific weakness of neck flexor muscles; myalgias present in <30%; *inclusion body myositis:* more likely to affect distal muscles, asymmetrically; cutaneous manifestations include violaceous eyelid rash (heliotrope); also pink, paper-like, scaly changes over knuckles, (Gottron patches or Gottron's papules) in dermatomyositis — pink to violaceous, scaly areas over knuckles, elbows, knees; cardiopulmonary manifestations include hypertension, arrhythmia, heart block, cardiomyopathy, congestive HF, pericarditis, respiratory failure, MI, interstitial lung disease, aspiration pneumonia (related to dysphagia), cancer; GI symptoms include dysphagia, malabsorption, acute gastric dilatation; association with malignancy, especially for older individuals — commonly lung and breast, but any organ can be affected; insufficient response to therapeutic intervention should stimulate evaluation for malignancy

Evaluation: CPK, aldolase, ESR, CBC, electrolytes, BUN, lactic dehydrogenase, creatinine, liver enzymes, calcium, magnesium, TSH, urine microglobulin, urine myoglobin, urinalysis; electromyography, and electrocardiography; CPK and liver enzymes may be elevated; *autoantibodies:* aminoacyl-tRNA synthetase (ARS), anti-Jo-1, nuclear Mi-2 (major protein of nuclear complex), signal recognition particle (SRP), anti-PM/Scl (associated with scleroderma), anti-Ku antibodies (associated with connective tissue disease), small nuclear riboprotein antibodies (snRNP), cytoplasmic ribonucleoproteins (RoRNP) antibodies, as well as TIF-gamma, anti-SSA, anti-RNP, and several other antibodies; ANA and RF seen in ≤50% of patients; statins associated with anti-HMGCR autoantibodies; *imaging:* MRI may demonstrate polymyositis, interstitial lung disease, and malignancies; chest radiography and high-resolution chest CT can identify pulmonary involvement and malignancy; also mammography, pelvic ultrasound, and upper and lower GI endoscopy; *electromyography:* increased insertional activity, fibrillation potentials, positive sharp waves at rest, decreased amplitude and duration of action potentials, increased polyphasic potentials, and/or bizarre high-frequency repetitive discharge; *muscle biopsy:* inflammation, necrosis, regeneration, endomysial infiltration by mononuclear cells; role of muscle biopsy problematic, as insurance reimbursement approximately 10% of cost; biopsy includes hematoxylin and eosin staining as well as staining for multiple enzymes; electron microscopy may also be needed; inclusion body myositis histologically similar to polymyositis, but with intracytoplasmic inclusion bodies; differential diagnosis extensive; can be divided into noninflammatory and inflammatory processes.

Noninflammatory processes: hypo- and hyperthyroidism, hyperparathyroidism, hypophosphatasia, Cushing disease (whether intrinsic or iatrogenic), medication effects, myasthenia gravis, Eaton-Lambert syndrome, tick paralysis, amyotrophic lateral sclerosis, fibromyalgia, congenital disease

Inflammatory processes: include those related to PMR, sarcoidosis, eosinophilic myositis, myopathies related to SLE, RA, Sjögren syndrome, polyarteritis, Behçet disease, and drugs, including alcohol, statins, antiviral agents, colchicine, procainamide, phenytoin, ketoconazole, other azole antifungal agents; parasitic infections, including toxoplasmosis, trichinosis, and cysticercosis; viruses, including Coxsackie virus, influenza virus, and HIV; and bacterial infections, including Lyme disease

Management: prednisone, methotrexate, IVIG, and rituximab; tacrolimus, mycophenolate also options; ACTH gel effective

Prognosis: polymyositis responds well to treatment, but residual weakness occurs in 30%; 5-yr survival 80% except with advanced age, pulmonary involvement, and malignancy; *poor prognostic indicators:* delayed intervention, older African-American individuals, females, cardiac and pulmonary involvement including interstitial lung disease, dysphasia, dysphonia, anti-SRP and anti-Jo antibodies; consultation recommended if ESR and TSH are normal, or if patient unresponsive to initial steroid therapy

Fibromyalgia

Background: controversial to diagnose; prevalence dependent on diagnosis; if any regional pain diagnostic criterion, frequency 20%; if widespread pain is criterion, frequency 11%; chronic fatigue — overlapping phenomenon, present in 20% of population; diagnosis includes chronic regional or widespread pain; initial diagnosis was based on presence of trigger or tender points, with prevalence in 3% to 5% of women and 0.5% to 1.5% of men; in rheumatologic practice, ~15% have tender or trigger points; considered a neurosensory disorder characterized in part by abnormalities in pain processing

Evaluation: no laboratory tests for definitive diagnosis; overall diagnostic criteria fail to exclude individuals with allodynia, in which touch perceived as pain; also does not exclude reflex dystrophy; history and physical exam needed; rule out hypothyroidism via TSH

Management: stress reduction and restoration of normal REM stage 4 sleep — zolpidem (Ambien, Stilnox)

and temazepam (Restoril); conditioning exercises important; pregabalin has some efficacy, although insurance companies often require gabapentin instead — interestingly, not approved for treatment of fibromyalgia; trigger point injections with lidocaine 1% can be effective; selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants have statistical beneficial effect — roughly one-third improve, but carry substantial risk of cardiac irritability, mortality, suicide potential; narcotics have no role in management; restoring stage 4 REM sleep cannot be achieved — narcotics block this stage

Sjögren Syndrome

Background: affects 0.1% to 4% of population, predominantly women (9-fold); involves lymphocytic infiltration of exocrine organs

Presentation: xerophthalmia, xerostomia, vaginal dryness, parotid gland enlargement, palpable and nonpalpable purpura, urticaria, arthralgias, arthritis, myalgia, Raynaud phenomenon, leukopenia, anemia, lymphadenopathy, neuropathy, vasculitis, renal tubular acidosis, and lymphoma

Evaluation: anti-SSA and anti-SSB antibodies may be present; Schirmer test to assess eye dryness;

Treatment: mostly symptomatic; preservative-free eye drops hourly while awake; cyclosporine eye drops may not be necessary; oral and vaginal lubricants; if symptomatic treatment ineffective or if weight loss, rule out associated malignancy

Mixed Connective Tissue Disease (MCTD)

Background: affects 2 people per 100,000; more common in Native Americans — 6.4 individuals per 100,000; especially seen in patients aged 15 to 25 yrs; between 3:1 and 16:1 female predominant; pathophysiology — activation of toll-like receptors, B-lymphocyte hyperactivity, T-lymphocyte activation, immune response to modification of the U170-weight antigen, endothelial cell proliferation with lymphocytic and plasmacytic infiltration

Presentation: diffuse hand swelling — most important, acrosclerosis, Raynaud phenomenon, arthritis, arthralgias, esophageal dysmotility, myositis, lung fibrosis, anticardiolipin antibodies associated with pulmonary hypertension, pericarditis, mitral valve prolapse, conduction disturbance, leukopenia, protein-losing enteropathy, and sclerodermatous-type changes on capillary microscopy

Evaluation: diagnosis controversial; initially diagnosed on basis of high levels of anti-U1 RNP antibodies and snRNPs; however, antibody presence not limited to MCTD — may be misleading; can diagnose based on symptoms instead; many patients have characteristics of other disorders characterized as connective tissue diseases but do not fulfill criteria for any one specific disease; must be distinguished from overlap syndrome, in which >1 connective disease is truly present — involvement of >1 connective tissue disease carries worse prognosis than individual components

Management: mainly symptomatic — NSAIDs and hydroxychloroquine; occasionally, phosphodiesterase type 5 enzyme inhibitor or endothelin receptor antagonist for severe pulmonary hypertension required; consultation ideal to differentiate from overlap syndrome

Prognosis: MCTD has favorable prognosis; major complications related to cardiac involvement

Key Points

1. Large-vessel vasculitis includes giant cell arteritis, polymyalgia rheumatica, and Takayasu arteritis.
2. Medium-vessel vasculitis includes polyarteritis nodosa, primary angiitis of the CNS, and Kawasaki disease.
3. Small-vessel vasculitis includes ANCA- associated vasculitis and immune complex-mediated vasculitis.
4. Fibromyalgia is difficult to diagnose; treatments vary but should center around improving sleep and decreasing stress.

Suggested Reading

Amato AA et al: Inflammatory myopathies. *Continuum (Minneap Minn)*. 2013;19(6 Muscle Disease):1615-33; **Clauw DJ:** Fibromyalgia: a clinical review. *JAMA*. 2014;311(15):1547-55; **Kinney MA et al:** Small-vessel vasculitis. *Dermatol Ther*. 2012;25(2):148-57; **Weyand CM et al:** Immune mechanisms in medium and large-vessel vasculitis. *Nat Rev Rheumatol*. 2013;9(12):731-40.

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Interpretation of the Medical Literature

Thomas Payne, MD, *Professor of Medicine, University of Washington School of Medicine*

Importance: great accrual of new information; we need to be able to assimilate what's published in the medical literature and judge its value to our practice and to our patients; keeping up with literature and continuously learning — lifelong learning

Incidence and prevalence: *incidence* describes the number of people who contract a disease over time, divided by the population under study (a rate); *prevalence* describes the number of patients who have a disease at one point in time, divided by the number in the population (a proportion)

Risk: proportion of people who are initially free of disease who develop disease over a defined time period

Relative risk: you compare the odds for two groups against each other (eg, the risk for developing breast cancer between two groups of women); first group is women who have a mother, sister, or daughter who has breast cancer; the other group is those who do not have a close relative with breast cancer; relative risk for those who have family history is higher than those who do not have a family history of cancer; relative risk is reported as a percentage (eg, 10% more likely) and you may also hear this in the context of an article in the press (eg, crossword puzzles decrease your odds of getting dementia by 20%); that statement is referring to relative risk

Absolute risk: the risk of a group of people developing a given condition (eg, cancer) divided by the number of people in the population; an example of absolute risk would be that a woman living in the United States has an absolute risk of 12% of developing breast cancer in her lifetime; both relative and absolute risk are useful in certain contexts, but are different; if a condition is very rare and if a treatment reduces the likelihood of that condition even further, then the relative risk will be reduced; absolute risk of developing the condition with or without the treatment is already very low

Calculating absolute risk reduction: if 26 out of 100 people develop dementia in their lifetime, the absolute risk is 26 over 100, or 26%; we usually compare the risk reduction of people exposed to a treatment with those not exposed to that treatment; an example of absolute risk reduction is a study of the use of a medicine to reduce hip fractures; in the group who received placebo, the risk of having a hip fracture was 22 over 183 (the number of people in the entire population receiving placebo) or 2.2%; in those who were exposed to the medication, the risk was 11 over 139, or 1.1%; the absolute risk reduction was calculated as 2.2% minus 1.1%, or 1.1%; the relative risk was 1.1% divided by 2.2%, or.5; 50%; it shows a difference in the placebo and treated groups, with a 50% reduction in their risk, but the absolute risk reduction was 1.1%; this distinction is important for how we explain the results of studies to our patients

Test characteristics and predictive value: often expressed using a tool called a 2×2 table, which is basically a square with four corners in it; at the top is the presence of the disease, so the label on the column on the left of this 2×2 table would be "Yes," and the label on the top of the column to the right would be "No"; on the left hand side is test result; the first row is labeled "Positive" and the second row is "Negative"; this table represents the test result of positive in people who have the disease and who don't, and the same information for a negative test result; we usually label the cells of this 2×2 table in the following way: A — upper left; B — upper right; C — lower left; D — lower right; this is a useful construct for explaining the concepts of test characteristics and predictive value; you can find this online or in a textbook

Sensitivity and specificity: *sensitivity* is the likelihood that the test is positive in people who have the disease; in our 2×2 table, this would be expressed as A over (A plus C); *specificity* is the likelihood that the test is negative in people who do not have the disease; in our 2×2, this is D over (B plus D); sensitivity and specificity are characteristics of the test being examined; in clinical practice, we usually do not know if a person has the disease and that is why we order the test; we get back a result that is positive or negative; *positive predictive value* is the likelihood that, given a positive test, the person has the disease; using the 2×2 table, that would be expressed as A over (A plus B); if the test is negative, the likelihood that the person does not have the disease (*negative predictive value*) is D over (C plus D); this makes the relationship between sensitivity and specificity in positive and negative predictive value clear; the positive and negative predictive values are determined not only by the test characteristics (sensitivity and specificity), but also by how common the disease is; in the 2×2 table, the left column is the people who have the disease with positive and negative tests and the right column is people who do not have the disease; if you add up those columns (eg, A plus C), that's the number of people who have the disease; also the prevalence of disease in this population

Test characteristics and probability: sensitivity and specificity do not change based on prevalence, but the positive and negative predictive value do; a test may be positive but more likely to be a false positive if the disease is very rare; if the disease is common, it is likely that the positive test result represents a true presence of the disease; relationship between disease prevalence and

test characteristics is the fundamental concept of Bayes' theorem; it relates the positive predictive value to the test characteristics and the prevalence of disease in the population; *pre-test probability* means the probability that a person has the disease before you do the test; that is the same as the prevalence of the disease in the population; in 2×2 table, prevalence is (A + C) divided by (A + B + C + D); *post-test probability* — probability that a person has a disease, given the presence of a positive or negative test; post-test probability of disease in a positive result is the same as positive predictive value; pre- and post-test probability are equivalent to prevalence (pre-test probability) and positive predictive value (post-test probability)

Likelihood ratio: a simple ratio of two percentages; numerator is the prevalence of the finding or test result in patients with the diagnosis; denominator is the prevalence of the same finding or test result in patients without the diagnosis; a *positive likelihood ratio* describes how the probability of the disease shifts when the finding is present; a *negative likelihood ratio* describes how the probability of disease shifts when it is absent; will often see tables of likelihood ratio of various physical exam findings or laboratory tests; helps you appreciate the value of that finding in distinguishing people who have the disease from those who do not

Relevance of above concepts: useful in reading articles in medical journals; relative and absolute risk concepts also useful for discussing results that may appear in the press with your patients; common confusion is that relative risk may be dramatic, but the absolute risk may be low, and the headline focuses on the relative risk, but not on the absolute risk; concepts also relevant in the application of serial testing in people with common conditions; eg, a patient in whom you are considering the diagnosis of pulmonary embolism may have a history and physical findings that allow you to calculate their risk for this condition; scoring systems can allow you to stratify patient's risk; this can help in choosing from the variety of tests available, which may vary from simple, low-cost, low-risk tests to expensive and/or higher-risk tests; useful to know the characteristics of each test before you decide; you also can relate them to the person's likelihood of having the condition based on your history and physical findings; this is a good example of how all of these concepts intertwine; using the pulmonary embolus example, if you assess your patient to be at low risk, a negative result in a test with very high sensitivity, such as D-dimer, would indicate a very low likelihood that the patient has a pulmonary embolus, and you may choose to stop testing at that point

New England Journal of Medicine (NEJM) example: January 2019 article on vitamin D supplements and prevention of cancer and cardiovascular disease; there is a table in which there are reported outcomes for people who were exposed to vitamin D and those who were exposed to placebo; the number of people who were in the vitamin D group who developed cancer of any kind was 793 out of a denominator of 12,927; the number of people who developed cancer in the placebo group was 824 in a placebo group about the same size; there were differences in the rate of developing cancer, but the differences were very small; if you calculate the ratio of the number of people with cancer in the vitamin D group and divide it by the ratio of the number of people who developed cancer in the placebo group, you find that they're very close; the number is.96, and that number is so close to 1.0 that it is not possible to say that the use of vitamin D for the prevention of cancer makes any difference; the *hazard ratio* was 0.96; the *confidence interval* is a way of expressing the imprecision of this result; the confidence interval indicated that the true effect fell within a range of 0.88-1.06, which includes 1.0; given the size of the study and the effect seen, we conclude that there wasn't evidence that vitamin D reduced the incidence of cancer

Odds: *pre-test odds* are the pre-test probability of the disease divided by (1 minus the pre-test probability of disease); odds, in general, are ratios; can calculate the *post-test odds* using the same formula; the pre-test probability of disease is basically the same as the prevalence, and the post-test probability is the positive or negative predictive value; when you hear the term odds, it means a probability divided by (1 minus that same probability); odds of 1:2 would suggest that the likelihood of an event is only half the likelihood that the event will not occur, so that would be a probability of.33

Parametric and non-parametric tests: *parametric* methods are those that assume that the data arise from a normal distribution or near-normal distribution; a normal distribution is a bell-shaped curve; *non-parametric* methods do not make the assumption that the data are in a normal distribution; there are other methods that can be used for data that are not normally distributed (eg, those that have to do with rank or other ways to relate one group with another in a non-normal distribution); examples of parametric tests are one- and two-sample *t*-tests and analysis of variance; examples of non-parametric tests are the Mann-Whitney test, the Kruskal-Wallis test, or the one-sample Wilcoxon test; data are divided into several types; there are *categorical variables* (eg, whether or not someone is alive, whether or not they're re-admitted to the hospital) where patients are in one category or another; there may be others that have several options (eg, race, tumor type); *numerical data* are those that we encounter frequently in test results (eg, cholesterol values, the number of times someone has been pregnant, the number of times they have been in the hospital); other kinds of data that are often used in studies include time; an analysis of *time to event* is often seen when studies have to do with treatment for a serious illness such as cancer; categorical data are often associated with tests such as 2×2 tables and chi-square tests, whereas numerical data may be used in tests such as *t*-tests or analysis of variance; remember the different types of data that exist and what terms are assigned to them; basic distinction based on data distribution is whether the data are normally distributed (bell-shaped curve) or whether they're not normally distributed (eg, distribution that has what's referred to as a long tail to the right or a long tail to the left)

Statistical testing: tests a hypothesis; most studies begin with a formal hypothesis, referred to as the *null hypothesis*; often, there is an *alternative hypothesis* to the null hypothesis, which is the alternative or the opposite of the null hypothesis; hypotheses are mutually exclusive and exhaustive; for example, if we are studying the effect of a medication on blood pressure, our null hypothesis might be that the use of this medication has no effect on blood

pressure, and the alternative hypothesis would be that it does have an effect; we gather data to test this hypothesis, and we use statistical testing to help us determine which of those two hypotheses is supported by the data; we often hear reference to *type I and type II errors*, and to *p-values*; a *type I error* occurs when a null hypothesis is rejected, although it really is true; we usually set a boundary to when we would consider a type I error to occur, and by tradition, it's about 5%; this is referred to as the *α level*, and it's usually.05 or 5%; the α level is the probability of rejecting the null hypothesis when that null hypothesis is probably true; eg, a medicine we find may or may not influence the blood pressure of the population; our null hypothesis is that it does not affect blood pressure; type I error occurs when the null hypothesis is rejected, meaning we think it did have an effect when actually it did not; you see this reported in medical studies as a *p*-value, and the *p*-value answers the question, "If the null hypothesis were true, what would be the probability of obtaining a value of this type or larger by chance alone?"; it is possible that what we're seeing in the result is explained by chance, but the likelihood is low if the *p*-value is less than.05; this is a reflection of the fact that we, from one study, do not really have an absolute answer, but we do have a probability, and the probability may be very high that this treatment or this effect is actually occurring; it is also possible that the results reported were explained by chance

Study design: many ways that information can be gathered in research; all have advantages and disadvantages; *observational studies* are very common; an example would be a *case series*; a case series is a collection of case reports involving patients given a similar treatment; there may be detailed information about these patients, who may have received a treatment for some condition; if the condition is uncommon, this may be the most efficient way to describe the experience of people like these cases; you collect all that you can and describe their experience over time

Cohort study: another form of observational study is a *longitudinal study* over time of a group of people who share some defining characteristic; different from a case study in that you are picking people who are similar in some respect and following them all over time, gathering data serially; an example of a cohort study is the Framingham Study, in which people in Western Massachusetts have been followed for more than 50 years to determine whether they develop heart disease and, if so, what kind; information was gathered about these people (eg, cholesterol and blood pressure) when they become part of the cohort, and then they were observed to see whether they developed cardiovascular disease

Cross-sectional study: different than cohort study; both are observational studies, but cohort studies can be used to study incidence and other things that happen to the people in this cohort (eg, incidence of heart disease in the Framingham Study); cross-sectional studies determine prevalence; we determine what percentage of people in the population in this cross-section in time have the condition; we don't know anything about the incidence of the disease by looking at the prevalence in that particular population; a cross-sectional study may involve fewer logistics; it would not necessarily be an easy study, but you would not have to follow that group for a very long time; start with a cross-section and determine prevalence in that group, versus the cohort study, where you are gathering together people who share some characteristic and following them over time

Case-control study: another example of observational studies, but different than case series and cohort and cross-sectional studies; designed to determine if an exposure is associated with an outcome; gather a group of people who have the outcome of interest, and then you gather controls (people without the outcome); match the controls to the cases in some characteristics (eg, similar gender, similar age); look to see how cases and controls differ in being exposed to some exposure of interest; question asked in a case control study: "Is an exposure associated with an outcome?"; have cases and controls, and the question is, "Do these two groups differ in some exposure?"; an example of this is an article in *NEJM* on the effectiveness of bicycle safety helmets; cases were people seen in an emergency room in one of five hospitals who received care for head injuries,; controls were people who received care for non-head injuries in the emergency rooms of the same hospitals; question was, "What proportion of the people who received care for head injuries were wearing bicycle safety helmets, compared with the percentage in the group that didn't have head injuries?"; found that there was an 85% reduction in the risk of head injury in the group that was wearing helmets; this is not an experimental study, but allows us to gather some information about the association between an exposure and an outcome; particularly helpful if that outcome is uncommon

Experimental study design: best example is the *randomized, controlled trial* design; considered the source of the strongest evidence in clinical medicine; in a randomized, double-blinded, controlled trial, individuals are randomly assigned to receive the intervention or some inactive substitute; very important that the subjects not be aware of whether they have received the intervention or the placebo; also important that the people who gather data on the outcomes are also unaware of whether the subject received the intervention or a placebo; the fact that neither the subjects nor the observers know whether it is a placebo or an active treatment is where double-blinded comes in; the randomized element of the name of the study is that you start with a group of people and randomly assign them to placebo or intervention, which reduces the likelihood that some characteristic of the patient explains the outcome rather the intervention; reason is that there should be an equal number of people who have these characteristics in both groups; in a randomized, double-blind, controlled trial, neither the subject nor the person recording the results knows which arm of the intervention is being observed, so they are insulated from their belief in the power of the intervention; it is a very powerful study design; considered the gold standard; it is not always possible to use this design to answer a question about an intervention; if it is possible and the funding exists to conduct such a study, we have greater confidence that the outcome is explained by the intervention under study and not by some other factor

Cluster randomized trials: used frequently; differ from standard randomized controlled trials in that the unit of randomization is not the individual patient, but a group of subjects or clinics or some other group; commonly used in circumstances where it is not practical to randomize individual subjects; may be a social unit, clinic, or community that is the unit of randomization; done for a

variety of reasons, including administrative convenience, ethical considerations, to avoid contamination between groups, and in places where the intervention is naturally applied at the cluster level

Bias: randomized, controlled trials are the best way to protect against bias; relying solely on expert opinion introduces risk that we may be wrong about a recommendation; observational studies don't often allow us to determine causality; in most cases, they help us determine association, but not causality; it is compelling to hear that there is a more common outcome in people who, eg, drink caffeine or engage in some other behavior, but we have to remember that, without a large number of studies and careful analysis, we can't determine causality and distinguish it from association; the rooster crows in the morning and it is very strongly associated with the sun coming up, but the rooster does not cause the sun to come up

Other designs: most studies (especially those that are not randomized, controlled, and blinded) attempt to control for covariates or other factors that might explain differences in outcomes; limitation is that we attempt to control for known covariates, but covariates that we don't know are not controlled for; our ability to control for those variables mathematically is imperfect, so we need to bear in mind the limitations of studies that don't use a randomized, controlled design; doesn't mean we can't learn from studies without that design; must be aware of limitations of studies with no randomization or blinding; other designs common in the literature include *stepped wedge design* and *interrupted time series*; these will not be discussed

Groups which help in determining usefulness of study results or recommendations: the US Preventive Services Task Force (USPSTF) and others use levels of evidence and grading systems to classify studies according to their level of evidence; USPSTF uses grades A, B, C, D, and I; A means that the USPSTF recommends the service; B means that it is recommended, but the level of evidence supporting that recommendation is not as great as for grade A; C indicates that the task force recommends selectively offering or providing this service to individual patients using professional judgment, because there is at least moderate certainty that the net benefit is small; D indicates that the USPSTF recommends against the service; I means that there is insufficient evidence currently to balance the risks and harms, and so a recommendation cannot be made at this time; general rule of thumb is that a meta-analysis, in which large numbers of studies are gathered together to see where the preponderance of evidence lies, is considered to be a very strong way of determining whether an intervention or some sort of treatment is worthwhile

Clinical decision making and patient communication: useful to reflect on the fact that there are a large number of tests that we can perform, but that the fundamental source of information for most clinical decisions is really not much different than it was many years ago; it is the history and the physical findings; listening carefully to the patient's story and gathering history from other sources often is the most beneficial step in determining the pre-test probability for subsequent testing; in most cases there is no single test that makes taking history unnecessary; the outcomes that we are trying to prevent are weighted differently by patients; they have different values and different priorities; the utility of various outcomes may vary patient-to-patient (eg, being alive or having quality of life, being in pain or not being in pain); people differ widely on which outcomes they find to be the most important; the idea of shared decision making is that the patient is carefully and thoroughly involved, so that their utilities and their desires are reflected in the decision that is ultimately made; a large variety of tools available to allow patients to weight the desirability of different outcomes, and to better understand the pros and the cons of the options being considered

Decision aids: *decision analysis* is constructing a (sideways) tree, which has its root at the far left and all of the branches at the right; the root is the decision we're focusing on (eg, do we or do we not undertake a test); that is determined by the branches to the right of that root; at the very end we have outcomes and utilities assigned to those outcomes; decision analysis is a formal construct that is sometimes used in clinical care, but also used in making policy decisions; sometimes we aren't certain about the probabilities of various branches in this decision analysis tree, and so we vary the probability of the branches according to a reasonable range — referred to as *sensitivity analysis*; it strengthens the result of the decision analysis if the sensitivity analysis does not change the ultimate answer when one of the probabilities is taken to its reasonable extreme; other aids to decision making, some of which involve patient or physician interpretation of data, include prediction rules; great deal of interest in machine learning and other techniques that would allow enormous volumes of data to be processed to help make decisions about what is the likely outcome, diagnosis, or result (eg, imaging interpretation; evaluation of pigmented lesions that may or may not require biopsy to exclude melanoma); this is a rapidly developing area, and one in which we have to use caution to temper our enthusiasm

Other concepts: we have talked about the *p*-value and the fact that we use.04-.05% as the *p*-value for most studies reported in the literature; this is not the same as determining clinical significance; with a very large study with an enormous number of patients, it may be possible to detect a very small difference that has statistical significance but may not be clinically significant; *cost-benefit analysis* and *risk-benefit analysis* are extensions of decision analysis in which cost or risk are among the factors measured in deciding on an action

Visual aids: when we are discussing these concepts with a patient, it is helpful to have some sort of graphical or visual representation of the concepts so that those who are not familiar or don't have much experience can grasp what we are trying to convey; there are some great examples of laboratory results conveyed to the patient using visual aids; eg, in discussing with parents where their child falls on a spectrum of children of the same age, sometimes pictures of children of different habitus can allow the parents to compare their own child and understand whether their child is developing as expected or may be heavier or taller or shorter than expected

Number needed to treat: another important concept for communicating with patients and thinking as physicians; if we're doing a study of intervention, we usually have a control and an experimental group; we calculate the **event rate** of some outcome (eg, cancer) in the control group, and find that there is a rate of, eg, 8%; with the

experimental group, when exposed to something that we're studying, the rate may be 3%; the difference between the two is the *absolute risk reduction*; 8% minus 3% is 5%; another way of looking at it is in calculating the number of patients we would need to treat with this intervention to prevent one occurrence of the outcome of interest; this is the reciprocal of the absolute risk reduction; eg, we have an absolute risk reduction of 5%, 1 divided by.05 is 20; this means one needs to treat 20 people to prevent 1 person from getting the condition; the number needed to treat varies by intervention; the amount of time that the treatment is given may influence the number needed to treat; if you treat for longer, the number needed to treat may be less; there are tables in textbooks or journals that convert the control event rate and experimental event rate to absolute risk reduction and from there to number needed to treat; you can do this yourself quickly if you have those two rates by remembering that the number needed to treat is 1 over the absolute risk reduction

Key Points

1. A 2×2 table can be helpful for remembering and understanding the concepts of test characteristics such as sensitivity, specificity, and positive and negative predictive value; those are related to each other if we also consider prevalence in the population
2. Study design makes a difference in our confidence that the result being reported is not related only to association, but may be related to causality; strongest study design is an experimental design; best available today is a randomized, double-blind, controlled trial; helpful because it takes away the power of belief of both patient and investigator and leaves observation unbiased;
3. Levels of evidence are useful because they can put together evidence from many studies and distill it into recommendations;
4. Relative risk comparisons tend to exaggerate outcomes compared with absolute risks; when you're discussing risks with patients, use absolute risk so patient can tell whether the intervention they are considering may reduce a very rare outcome to much rarer or a fairly common outcome to substantially rarer;
5. Statistical significance does not equal clinical importance; especially true for large studies with uncommon outcomes

Suggested Reading

Manson JE et al: Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 2019 Jan;380(1):33-44; **Mellis C:** Lies, damned lies and statistics: Clinical importance versus statistical significance in research. *Paediatr Respir Rev* 2018 Jan;25:88-93; **Thompson RS et al:** A case-control study of the effectiveness of bicycle safety helmets. *N Engl J Med* 1989 May;320(21):1361-7.

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High Value Care, Patient Safety, and Quality Improvement

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Introduction: reimbursement models and electronic healthcare records and systems are constantly changing, but basic principles of quality improvement are always applicable; in 2019 and beyond, we have relatively new additional reimbursement systems; these systems were put in place by the Center for Medicare and Medicaid Services (CMS) in an attempt to switch from paying for reporting to paying for performance

Pay for Performance (P4P): considers whether time healthcare provider spends working with or patient results in a measurable improvement for patient via process or outcome measure; value-based purchasing; considers differences between paying for reporting (fee for service) and P4P

Knee arthroscopy: one of most common procedures worldwide; several studies have shown similar outcomes at one year with surgery or physical therapy without surgery; at least one study has shown faster progression to knee arthroplasty or knee replacement for individuals that have undergone knee arthroscopy; levels of knee arthroscopy for meniscal tear might be higher in a pay for reporting environment with potentially the same or worse outcomes

Hospital stays: consider switching from a system maximizing days in the hospital, which increases hospital reimbursement, to one that focuses on evidence as well as a component of minimizing hospital stays, as there is a finite pool of healthcare spending dollars available; hospitals may attest that the pendulum that has swung too far in the other direction; there are now far fewer patients meeting admission criteria, either by InterQual criteria or Milliman Care Guidelines (MCD); patients being admitted for much shorter stays, partially in an attempt to adhere to the evidence-based guidelines

CMS guidelines: address how many patients should be readmitted to the hospital due to complications or symptoms after discharge; hospitals can be penalized for exceeding these recommended limits

Perspectives: not clear that we are providing the safest and most effective individualized care by adhering to these evidence-based population guidelines; Dr. Peter Pronovost, director of the Armstrong Institute for Patient Safety and Quality at Johns Hopkins Medicine, notes that some readmissions aren't avoidable and some may be beyond the hospital's control, especially since patient adherence to a treatment plan also has an impact; various studies show potential negative or no impact to patients after implementation of the Hospital Readmissions Reductions Program (HRRP) by CMS; overarching concern is whether we are measuring the right things to positively impact patient care

Controversy: Dr. Donald Berwick, former director of CMS, wrote January 1989 article in *New England Journal of Medicine*, "Continuous Improvement as an Ideal in Healthcare;" has skepticism for proliferation of modern healthcare measures; in 1989 article, he noted importance of quality improvement for small systems, large systems, and individual physicians; origin of the theory of continuous improvement in Japan, proved itself in American industries; he and others have noted concern at the sheer quantity of modern quality measures; "complex incentives;" discussed in 2017 article in *Becker's Hospital Review* called "Five Big Missteps on the Patient Safety Journey;" concerns include considering money more important than safety, believing that safety has been achieved, thinking that incentives will improve safety, and separating the concepts of quality and safety; 2017 University of Chicago study noted that 21% of patients report experience with medical errors; many medical professionals can agree to focus on important quality measures to avoid diverting precious healthcare resources away from important and potentially actionable information

Quality measures: two primary types, process and outcome; process measures are the specific steps in a process that lead either positively or negatively to a particular outcome metric, eg, pressure sores; as your institution needs to reduce the number of the pressure sores that develop in patients during a stay at your institution, the outcome measure would be pressure sores and a process measure might be the number of times an immobile patient is turned by a staff member during the day; another process measure might be how many patients with immobility are provided with a bed or mattress that might reduce the risk of pressure sores; both process and outcome measures might be important; ultimately the most impactful measure is what actually happens to the patient (the outcome measure); we often hope that the process measure predicts the outcome measure, but this is not always the case; if staff members spend too much time logging process measures, they may not have the time for patient care such as turning the patient

Root cause analysis: another way to try to improve outcome measures; consider how you reduce pressure sores for ulcers; question depends on what causes them; immobility is one clear risk factor and poor nutrition might be another; institution might be obtaining data to determine what other factors might play a role in your setting; learning

environment plays an important role in solving problems; consider what data you are gathering and how you are sharing that data to come up with solutions; consider what role the is system playing to solve the problem; in this example, the system may have a policy that patients with immobility must be turned every two hours in the hope of preventing pressure ulcers; system policy and individual responsibility is likely best prevention against error

Swiss cheese model of error: for patient error to occur, multiple errors must occur and not be caught either by the system or the individual; in theory, systems are set up so a single error would always be caught and not translate to an error that results in patient harm; most often, it is the process, not the person, that fails

Checklists: from aviation, we know that humans are capable of error, particularly in very simple, frequent tasks; what works best to prevent this is system checks to ensure that the simple processes are not missed or done incorrectly; checklists are one way to ensure this; many studies have supported the life-saving nature of processes and checklists, including avoiding seemingly obvious problems such as wrong-site or wrong-patient surgery; have been shown to be effective at many other procedural complications, such as reducing catheter-associated blood infections; decision support, which is the ability to have help making decisions, has been provided in the past for multiple forms of checklists and algorithms; we are heading towards forms of artificial intelligence to help with decision making as well as to reaffirm or dispute diagnoses and treatment plans based on available evidence

Bias: multiple forms of bias unconsciously enter the cognitive decision process; for example, recency bias tends to favor a more recent diagnosis; tools and access to recent evidence can help obviate these biases and hopefully lead to more correct diagnoses

Medicare Access and CHIP (Children's Health Insurance Program) Reauthorization Act of 2015 (MACRA)

Introduction: newer payment models attempt to pay more for performance than quantity of medical care; growing pains due to multiple hindrances, such as variance in data collection, multiple electronic medical records; some are using paper records; MACRA is utilized by CMS; sets the payment system for doctors who treat Medicare patients; has limitations; not all providers are beholden to MACRA; created in association with repealing the Sustainable Growth Rate Formula (SGF), which had previously determined Medicare Part B reimbursement rates with the attempt to provide, at least in part, a payment for performance system; MACRA or the Quality Payment Program (QPP), is based on two reimbursement structures; these are the Merit-based Incentive Payment System (MIPS) and Advanced Alternative Payment Models (APMs or AAPMs); providers usually fall into one category or the other; MIPS combines part of the old Physician Quality Reporting System (PQRS), part of the value modifier or value-based payment modifier (VM), and the Medicare electronic health record (EHR) incentive programs into one

Payment: under MIPS, eligible professionals (EPs) will be measured and paid on components; each of these components gives you a score; you can get bonuses; this all factors into reimbursement for Medicare, which is plus or minus seven percent of your total intake in 2019; exceptional performers that meet the additional performance threshold could receive an additional sliding scale positive payment adjustment of up to 10%; physicians participate as individuals or as groups; components are quality, cost, clinical practice improvement/electronic health record, and improvement activities; percentage of each of these components varies per year; in 2019, quality is 45%, cost is 15%, clinical practice improvement/electronic health record is 25%, and improvement activities is 15%

Quality: clinicians must report six measures, including one outcome measure; eligible clinicians can earn two bonus points for each additional outcome and patient experience measure reported and one bonus point for each additional high-priority measure reported; there are bonuses on top of the baseline; basically we have the Consumer Assessment of Healthcare Providers and Systems (CAHPS); it's optional; if you report it, it counts as one quality measure; in the six self-reported measures, CMS will calculate the all-cause hospital readmission measure for groups of 16 or more clinicians with at least 200 cases; this measure evaluates the readmission rate for beneficiaries 65 or older who are hospitalized at a short-stay acute care hospital and experienced an unplanned readmission for any cause to an acute care hospital within 30 days of discharge; have multiple measures; each measure worth up to 10 points; the maximum points available for the quality category depends on the clinician's group size or submission mechanisms

Examples: group of 115 eligible clinicians, in which case you have six measures and 10 points per measure up to a maximum of 60 points; if group of 16 or more eligible clinicians, then you have six measures with 10 points per measure plus you have to now factor in all-cause hospital readmissions, which multiply by 10 points for a total of 70 points

Other calculation approaches: if a clinician reports more than six quality measures, CMS will use the six highest to calculate the quality score; reporting more quality measures can be beneficial; clinicians can earn two bonus points for each additional outcome and patient experience measure reported and one bonus point for other high priority measures; other high priority measures are defined as appropriate use, patient safety, efficiency, and care coordination measures; bonus points are capped at 10% of the total quality score

Resource use (cost): for this, there's no data submission required; CMS calculates the cost using claims data; measures include Medicare spending per beneficiary and total per capita cost; working on developing new episode-based cost measures for use in future program years

Clinical practice improvement: largely EHR; used to be called meaningful use; was concerned with promoting interoperability; these measures have a base score and a performance score; reporting additional measures can increase the performance score

Improvement activities: include things like ongoing care coordination, clinician and patient shared decision making, regularly using patient safety practices, and expanding practice access; in the 2018 performance period, MIPS-eligible clinicians will be able to choose from more than 100 activities to show their performance

Hardship exemptions: available for all of these measures that we discussed above; based on, for example, insufficient internet connectivity for the EHR scoring; can cause reassignment of the weight, for example, of the EHR measure to something else, such as the quality measure; failure to report any of the required base measures will result in a base score of zero and a performance category score of zero

Requirements: MIPS-eligible clinicians and groups would have to earn at least 30 MIPS points, which is up from 15 points in 2018, to ensure a neutral payment adjustment; no increase or decrease in pay from CMS; CMS raises the bar for the top MIPS performers; clinicians in groups seeking an exceptional performance bonus would need to earn at least 75 MIPS points, which is up from 70 points in 2018

Changes: addition of a small-practice bonus; a small practice, which is 15 or fewer clinicians, can receive a five-point bonus added to their MIPS final score; complex patient bonus; means that eligible clinicians can earn up to five bonus points to their final score providing care to complex patients; size of this bonus is based upon average hierarchical condition category (HCC) risk scores and proportion of dual eligible patients; increased low-volume threshold; eligible clinicians who provide care to less than or equal to 200 Medicare Part B beneficiaries, or receive less than or equal to $90,000 in Medicare Part B payments, are excluded from MIPS; can check your status on the website for CMS; longer performance period; performance period for the quality and cost categories is a full calendar year; January 1st through December 31st, 2018; performance period for improvement activities and promoting interoperability categories is any consecutive 90 days

Eligibility: determine whether clinician will be included or excluded from MIPS; clinicians that are excluded from MIPS include those with few Medicare Part B patients (as described above); eligible clinicians in their first year of participation in Medicare; qualifying and partial qualifying Advanced Alternative Payment Model participants who qualify for AAPM bonus; partial QPs, or people that have that partial qualifying bonus, may elect to report to MIPS; MIPS-eligible clinicians will receive a 0.25% increase in their physician fee schedule beginning in 2026

Eligible clinicians: types besides doctors remain the same in 2018 with the following additions, including physical therapists, occupational therapists, clinical psychologists, qualified speech-language pathologists, qualified audiologists, and registered dietitians

Advanced Alternative Payment Models: second possible payment track under MACRA; similar to previous accountable care organizations; thought to represent a much smaller percentage of eligible clinicians

Examples: Comprehensive Primary Care Plus model, Medicare Shared Savings Program model, Medicare Accountable Care Organization (ACO) Track, Next Generation ACO model, and Vermont Medicare ACO Initiative; additional models will be announced by CMS as they are approved

Eligibility: eligible clinicians in MIPS and APMs are not eligible for the annual AAPM five percent lump sum bonus payment; may qualify for positive MIPs payment adjustments and exceptional performance adjustments based on the APM entity's final score; under the APM scoring standard, eligible clinicians (ECs) are subject to MIPS reporting requirements and payment adjustments

Scoring: to ease reporting burden for quality performance categories, CMS will use the APM quality data submitted by the MIPS APM on behalf of the participating MIPS-eligible clinicians; past performance category is scored at zero percent for MIPS APM participants; CMS will assign each MIPS APM an improvement activity score based on the APM model design and how it compared with the improvement activities available; MIPS APM are only required to self-report the promoting interoperability performance category under MIPS, as other categories are not subject to reporting requirements, or the CMS will draw data from other sources; for example, with APM for quality, CMS will use data submitted to the CMS web interface on behalf of participating MIPS APM-eligible clinicians to assess the quality category; for cost, use zero percent as that performance category weight and not assess MIPS-eligible clinicians based on cost; for improvement activities, CMS will assign a score based on the requirements of the MIPS APM compared to the improvement activities requirements; for the performing interoperability requirement, all individuals in the MIPS APM will need to submit data for the PI (promoting interoperability) requirement, which will be 30% of the total score

Focusing on measures of value for patients: American College of Physicians in collaboration with other organizations has a worldwide initiative to promote the practice of high-value care with the goal of improving outcomes by providing care with proven benefit that also reduces cost by avoiding unnecessary, risky, or harmful interventions; value is very important in healthcare quality improvement and generally refers to quality over cost and sometimes quality plus outcomes over cost; can find various accessible curricula online; important to review or evaluate what other organizations, like ACP or the Cochrane Library, have reviewed; consider current evidence about an area such as diagnostic tests and treatments to include potential harms, costs, and benefits; need to choose interventions that maximize benefits, minimize harms, and reduce costs while eliminating diagnostic tests and treatments that provide no benefit or may be harmful, while incorporating patient values into care plans; helpful if providers work at the systems level when possible to update and incorporate high-value care options based on the most recent available evidence

Patient Safety

Introduction: patient safety is generally defined by the World Health Organization as the absence of preventable harm to a patient during their process of healthcare and reduction of risk of unnecessary harm associated with healthcare to an acceptable minimum; recognize where cognitive error, such as bias, is influencing patient care

Heuristics: cognitive errors involve heuristics, which are often referred to as rules of thumb, educated guesses, or mental shortcuts; heuristics usually involve pattern recognition and rely on a subconscious or intuitive integration of patient data with prior experience rather than on a conscious and more logical generation of a

rigorous differential diagnosis based on specific data from the literature; these errors can create blind spots and care confirmation bias, also known as cherry picking, looking for evidence to support your conclusion and ignoring evidence that does not support your conclusion instead of open-mindedly looking equally at all available evidence

Contributing factors: often influenced by time; in a rushed environment it is more difficult to be open-minded to a variety of possibilities; another example is gender bias, which may be unconscious; there's evidence that women are less likely than men to receive more advanced diagnostic and therapeutic interventions

Other cognitive errors: include premature closure (jumping to conclusions); can be exacerbated by time pressure; attribution errors where you make conclusions based on a stereotype; triage queuing where previous decisions that were made in the healthcare chain, such as who a patient was referred to, creates care plans different than what would be created if the provider were evaluating the patient without the previously provided information

Avoiding errors: 1) recognize the possibility of them occurring and be mindful of the possibility so they can be corrected; 2) allocate appropriate time to the processes of diagnosis and treatment planning so that you don't feel rushed; 3) keep up to date on the available evidence and look up information when needed; 4) ensure that you are not sleep deprived or impaired in any way when making clinical decisions; avoid distractions; 5) have a strict, logical methodology that you always follow to arrive at a diagnosis or plan; 6) be your own devil's advocate; argue with yourself against your own conclusion and see if you can find any holes in your theory or alternative explanations

Medication errors: ripe opportunity for improvement; defined as a preventable event with medication administration that can lead to harm or an adverse drug event (ADE); per the Agency for Healthcare Research and Quality, ADEs account for nearly 700,000 emergency department visits and 100,000 hospitalizations each year; nearly five percent of hospitalized patients experience an ADE, making them one of the most common types of inpatient errors; usually several locations in patient care where ADEs can be halted; these include physician prescribing, pharmacy checks, patient or patient advocate checks, nursing awareness, information located on the medication; blood thinners, such as heparin, are one of the most dangerous medication types in the inpatient setting; as a system, want to have a lot of safety checks along the path of a medication from being prescribed to when it is administered to the patient; special attention must be paid to polypharmacy, when there are many drugs being prescribed that can potentially interact with each other; similar-named drugs, also known as the look-alike, sound-alike conundrum; patients with organ impairment, such as kidney or liver problems

Transitions of care: another chief area of risk; when patients are being moved; may be from one area of the hospital to another, from one hospital to another, or from hospital to home; even when patient care is being changed from one provider to another, miscommunication can result in serious patient harm

Mitigation: effective communication; many communication transfer tools; Situation Background Assessment Recommendation and Question (SBARQ); listening to all of the five P's; I-PASS (Illness severity, Patient summary, Action list, Situation awareness and contingency planning, Synthesis by receiver); may be helpful to familiarize yourself with these, find the one you're most comfortable using, and stick with it as your primary communication tool when facilitating transfer of care; effective medication reconciliation is important; make sure that medications are appropriately evaluated and reconciled in multiple steps along the transition points as well as order entry

Quality Improvement

Introduction: important to understand basic processes and techniques that you can apply to situations or problems to obtain solutions or improvement; total quality management is umbrella term; in medicine, we usually refer to this as just quality improvement or continuous quality improvement (CQI), with the understanding that multiple or continual iterations of improvement are usually required

Three general principles as applied to medicine: 1) orient all efforts towards improving patient care and removing waste such as unnecessary time or spending; 2) stress team effort and cooperation at all levels, because healthcare is a system and depends on people at multiple levels to ensure timely and effective care to reduce error; 3) use data and scientific reasoning to guide and evaluate improvement efforts; in general, quality improvement is trying to improve value, as discussed earlier, increasing benefits and reducing cost as well as errors

Approaches: checklists are one way to reduce waste and errors; Dr. Edwards Deming had enormous influence on the Quality Revolution; worked with Dr. Walter Shewhart of AT&T Bell Laboratories; created a list of 14 points of quality improvement/principle; includes improving constantly and forever the system of production and service to improve quality and productivity and thus constantly decrease cost; in medicine, the system of patient care and the birth of continuous quality improvement is from this movement; institute training on the job and institute a vigorous program of education and self-improvement; break down barriers between departments, which is still a large issue today; remove barriers that will rob people in management and in engineering of the right to pride in workmanship; put everybody to work to accomplish transformation

Models of quality improvement: be familiar with the basic tenets of these models/structures to organize CQI; idea of STEEEP (see below) to achieve the triple aim; triple aim was established by the Institute of Healthcare Improvement (IHI); primary goals of healthcare include 1) improving the patient experience of care, quality, and satisfaction; 2) improving the health of populations; 3) reducing the per person cost of healthcare; Institute of Medicine (IOM) created a list of six domains of healthcare quality, which can be shortened to the acronym, STEEEP, as a framework to evaluate CQI processes and goals

STEEEP: Safe — avoiding harm to patients from the care that is intended to help them; Timely — reducing waits and sometimes harmful delays for both those who receive and those who give care; Effective — providing services based on scientific knowledge to all those who could benefit and refraining from providing services

to those not likely to benefit; Efficient, which means avoiding waste, including waste of equipment, supplies, ideas, and energy; Equitable — providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status; P, patient-centered; providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions

Plan, Do, Study, Act: IHI created from original Deming-Shewhart PDCA cycle, also known as Plan, Do, Check, Act; concept is that for every potential quality initiative, you should plan it out carefully, implement it, study the effectiveness or lack thereof, and then make changes as necessary prior to repeating this cycle, if it turns out to be worth repeating

Eliminating waste: two very pivotal systems that have changed historically are called Lean and Six Sigma; one of key points of both systems is to eliminate waste; Lean evolved from the Toyota Production System with an attempt to eliminate waste from manufacturing; Six Sigma originally came from Motorola with a goal of eliminating waste or defects

- Waste: wasting of time of patients or providers; manual processes that could be effectively automated; wasting time looking for things, such as medical records that could have been more available, or other patient information that could have been more accessible with a better designed system; defects, errors, harm, unnecessary cost; example is providing a service that has no benefit; excess or unnecessary equipment

Helpful tools: process mapping and/or fishbone diagramming; process mapping is a general tool of what are all the components of a particular process; usually mapped out in diagram, which could be a fishbone diagram; often, this allows for the process owner or the primary person responsible for the process to see things they may not have realized before; benefits from the input of everyone involved in the process; allows for mapping out of various steps as well as alternative steps and errors in time involved, also referred to as cycle time; provides a starting point for which potentially to make changes and most importantly, to go back and see whether a change was or was not an improvement

- Fishbone diagram: the lines often look like the skeleton of a fish; specific type of process mapping; also called a cause and effect diagram; adopted by Dr. Edwards Deming; effect is the problem you're working on, so a fishbone diagram is problem oriented; the spine, which is a horizontal line of the fish, points towards the main problem being addressed; lines off the primary line designate other involved processes; team involved in all of these processes around the problem can work on brainstorming until the fishbone diagram is compete; then potential solutions can be discussed

Macro level: "patient-centered medical home" is a team-based healthcare delivery model with the goal of maximizing beneficial patient care outcomes by focusing on coordination of care; keep the end results in mind, such as patient health, function, and survival; members of the medical home work together, sometimes sharing risks and rewards to improve and maintain patient health; model that is currently being explored as a mechanism to improve overall patient care; one extension of this model is the "patient-centered medical neighborhood;" includes partnerships between hub of patient care, which is often primary care, and the spokes, which is often specialty care; models depend on sharing and coordination of patient information in way that maximizes benefit to patient

National Patient Safety Goals: created as an effort by The Joint Commission, which is an organization that routinely reviews and accredits, when appropriate, healthcare organizations and services; accreditation refers to validation of standards, for example, as safe and appropriate or effective; goals divided into several distinct areas; often involve attempting to reduce risk of error; for example, identifying patients correctly requires that providers have at least two ways to identify patients such as date of birth and name; preventing infection involves appropriate hand hygiene; preventing mistakes in surgery involves pausing before surgery to discuss details, also known as a time-out, to ensure everyone is on the same page as well as actually marking the site of surgery, which reduces the risk of wrong-site surgery

Suggested Reading

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Routine Care of the Healthy Patient

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Periodic health exam: the health exam of the healthy patient who is not being treated for chronic illness focuses on preventive health measures that have been accepted as cost-effective for the general population; these principles should be applied to patients with chronic medical conditions as well; a systematic approach is necessary to ensure the exam opportunities are going to be capitated under the capitated models of reimbursement; the periodic health exam is an area where ineffective practices have been all too common; lecture will review evidence-based screening tests with focus on cost-effectiveness and avoidance of unnecessary testing; key reference is US Clinical Preventative Services Task Force ("USPSTF" or "Task Force"); also the American College of Physicians guidelines and "high value care statements"; also "Choosing Wisely" program (choosingwisely@abim.org) from American Board of Internal Medicine (ABIM) Foundation, which is aimed at avoiding unnecessary tests, treatments, and procedures

Goals of periodic medical exam

Establishing a rapport with the patient: relationship building is critical; begin by greeting the patient — shake their hand, tell them your name, make eye contact, assume a seated position at eye level with the patient; when you're talking with them about their periodic health exam, you're beginning to establish a rapport; if it's somebody you already know, you're going to engage in small talk about their family, their children, their work, what's important to them in their life; if it's somebody you don't know, you're getting acquainted with them on this level, getting to know their demographic or work situation better; once you've established a rapport, you can begin to develop a trust relationship that will help you engage them for lifestyle change

Patient self-inventory: hopefully, you have had a chance to do some clinical assessment before the patient enters the exam room through the administration of a patient self-inventory of past medical history and review of systems on a tablet, and you can use that to begin to populate your electronic health record; it's critical to begin to validate all of this information once you receive it, whether the data is self-collected by the patient or taken by someone else in your office;

Family history: particularly important in the periodic health assessment, because it may help guide your choice of screening tests, or indicate the advisability of genetic testing; pay attention to family history of cardiovascular disease, hypertension, stroke, cancer, diabetes, and other chronic diseases;

Health behaviors: need to be thoroughly reviewed, including lifestyle issues such as diet, exercise, specific sports, and review of habits, including tobacco, marijuana, street drugs, and alcohol; a careful sexual history should also be taken, including the number of lifetime sexual partners and whether straight sex, gay sex, or bisexual sex is preferred; remember there are 3 things in the history that you need to find out: what the patient knows and tells you, what the patient knows and doesn't tell you, and what the patient doesn't even know to tell you; this is particularly true with drug use or signs of physical or emotional abuse; for abuse, you may want to consider an ACE (Adverse Childhood Experiences) Score, which digs back into the early history for signs of toxic stress; find it on NPR.org; it greatly affects chronic morbidity and mortality, so it is good to have available for your patients;

Medication review: must include over-the-counter medications as well as herbal supplements; note allergies to any medications or over-the-counter supplements; a travel history and an occupational history are important; complete review of systems must be taken, and we must review it ourselves

Vital signs: we need height and weight to calculate the basic metabolic index (BMI); patients with an excessive BMI >30 need weight management and exercise and dietary advice; accurate blood pressure must be recorded; the ICD-CM (International Classification of Diseases 10 — Clinical Modification) guidelines must be followed and a resting heart rate must be recorded; JNC 9 (Joint National Committee 9) guidelines are used for blood pressure;

Physical examination:

Sports physical exams: can be tailored to the specific sport; persons participating in rigorous physical activity may need to have more specific maneuvers to rule out certain cardiac conditions such as asymmetric septal hypertrophy or hypertrophic cardiomyopathy;

General physical exam guidelines: it is important to examine head, eyes, ears, nose, and throat; apply blood pressure guidelines according to JNC 9; check for carotid and abdominal bruits; perform complete cardiac exam and pulmonary exam; check for signs of organomegaly; do digital rectal exam, particularly in certain age groups; obtain self-vaginal smear by women versus a pelvic exam or HPV (human papilloma virus) reflex test (there is new evidence suggesting that the self-exam is adequate); complete musculoskeletal exam, neurologic exam, skin exam, hearing and vision oral health; do

emotional and functional assessments in the elderly, with anticipatory guidance; it is particularly important to pay attention to social isolation in the elderly; perform musculoskeletal exams specific to sports, such as attention to hips and knees in runners; carotid artery screening has not been found to be of significant value — this is explained in the High Value Care statements; I always like to include pronator drift for neurologic exams; begin by looking at the US Clinical Preventive Services Task Force (USPSTF) for adults, the American College of Physician Guidelines, and the American Board of Internal Medicine;

Laboratory tests, look at the age-specific guidelines and specific college guidelines; for lipids, I include the American College of Cardiology; look at the strength of evidence recommendations and review the outline of key tests, including cancer screening and infectious disease screening; a High Value Care statement on the periodic health exam discusses increased delivery of preventive services for which there is no evidence of any benefit in reduced morbidity or mortality; overall, we can't say that periodic health exams are shown to make a difference in morbidity and mortality; however, the specific screening tests that we can conduct will have evidence to support them according to the USPSTF

Principles of screening: to identify signs of infectious diseases such as TB and sexually transmitted diseases; to identify substance abuse conditions that have a high prevalence in the population today, such as the epidemic of opioid abuse; to identify cancers that have a high incidence by screening that is age-appropriate for the various cancers (prostate cancer in men, colon cancer in both genders, breast cancer — more predominant in women, but breast cancer can happen in men too); to identify signs of chronic disease, including cardiovascular disease, cerebrovascular disease, diabetes, neurologic disease, obesity, arthritis, hepatitis, pulmonary disease, endocrine disease, and renal disease

When do we stop certain screens?: patients who reach a certain age may not benefit from certain screens; guidelines state that women over the age of 75 may not benefit from having a mammogram, and men over the age of 70 may not benefit from having a PSA (prostate-specific antigen) test; screening tests based on the guidelines must be individualized and part of a shared decision-making model with patients in such cases as PSA tests or mammograms for women between 40 and 50

Screening tests that are not recommended by the USPSTF (Low Value Care statements): routine urinalysis; EKG in asymptomatic patients; cardiac CT calcium scores; carotid stenosis screening; AAA (abdominal aortic aneurysm) screening in women; PSA screening, particularly in certain age groups; ovarian cancer screening with CA 125; CA 99 for pancreatic cancer screening — there's no value in pancreatic cancer screening; spirometry in asymptomatic patients; genetic testing for hemochromatosis; chronic hepatitis B in asymptomatic patients

Recommended routine screening: mammograms between ages 50 and 75; colorectal cancer screening; perhaps a CT scan of the chest with ultrafine CT for lung cancer in long-term smokers over the age of 55

Task Force gradations and definitions: Grade A means the service is recommended; there's excellent evidence of benefit from this service; Grade B, the service is recommended; there's a high certainty that the net benefit is moderate to substantial; Grade C, the recommendation is to offer this service to individual patients based on professional judgment and patient preferences; there's at least some certainty that there is a small net benefit; Grade D, the Task Force recommends against the service; there's moderate or high certainty the service has no net benefit and the harm outweighs the benefit; (recently prostate-screening switched back from D to C); Grade I means there is currently insufficient evidence that the balance of benefits and harms falls on one side or the other; patients should understand the uncertainty

Chronic disease screening — diabetes: should screen for abnormal glucose and diabetes, specifically type 2 diabetes, in people aged 40 to 70, particularly those who are overweight; glucose screening is recommended as part of cardiovascular risk assessment in adults aged 40 to 70 who are overweight or obese (BMI is ≥30); offer this as part of the metabolic screen and refer patients with abnormal blood glucose to intensive behavioral counseling to promote a healthy diet and physical activity; these are the patients who are most predisposed to metabolic syndrome; this is given a grade B according to the Task Force

Chronic disease screening — hypertension: screening for high blood pressure following the JNC 9 guidelines in adults aged 18 and older is recommended; measurements should be obtained outside the clinical setting for diagnostic confirmation before starting treatment; we all know about white coat hypertension; let's see what the patient looks like when they're at home and they're in a resting situation; this is a grade A recommendation;

Chronic disease screening — obesity: the USPSTF recommends screening all adults for obesity; clinicians should offer or refer patients with a BMI of 30 kg/m^2 or higher to intensive multi-component behavioral interventions; there is also a social-ecological model that goes well beyond the clinic, a multidisciplinary approach to help the patient lose weight; this has a grade level of B

Chronic disease screening — osteoporosis: screening is recommended for osteoporosis in women aged ≥65 years and in younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors; that has a grade B recommendation

Chronic disease screening — lipids: the USPSTF does not give clear guidance at this time; they have archived all the older recommendations, and the American College of Cardiology (ACC) guidelines are being updated; to be prudent, we should be more aggressive in testing lipid levels in cases where there is a personal or family history of hypercholesterolemia, excessive BMI, or any of the risk factors for cardiovascular disease — hypertension, smoking, diabetes, metabolic syndrome, etc; ACC guidelines are probably the most stringent and are due to be released soon; keep an eye out for the ACC guidelines — a discussion of these is available at acc.org

Chronic disease screening — abdominal aortic aneurysm (AAA): for men aged 65 to 75 years who have ever smoked, the Task Force recommends one-time screening for AAA with ultrasonography; this has a

grade B recommendation; for men aged 65 to 75 who've never smoked, the Task Force recommends selective screening, rather than screening all men; this is a grade C recommendation

Chronic disease screening — STIs: we offer baseline HIV and STD testing for all adults as part of lifestyle medicine guidance; for syphilis, in asymptomatic, non-pregnant adults and adolescents who are at increased risk of syphilis infections, screening is recommended; that is given an A recommendation from the USPSTF; USPSTF recommends chlamydia and gonorrhea screening for sexually active women 24 years and younger and in older women who are at increased risk of infection; this is a grade B recommendation for both groups; all adolescents and adults ≥15 years should be screened for HIV infection; younger adolescents and older adults at increased risk should also be screened, but a baseline test should be taken

Chronic disease screening — hepatitis: for those at high risk, hepatitis B screening receives a Grade B recommendation; we know that populations from Southeast Asia are at increased risk of hepatitis B as well as drug users and other populations; for hepatitis C, the current recommendation is for screening persons at high risk; this is a one-time screening for HCV in adults born between 1945 and 1965 (Baby Boomers); has a grade B recommendation

Infectious disease screening — tuberculosis: for asymptomatic patients who are at risk of infection, screening for latent tuberculosis (LTBI) is recommended for populations at increased risk, the homeless, immigrants, refugees, the elderly, etc.; has a grade of B

Substance abuse screening: the USPSTF recommends that clinicians screen adults aged 18 or older for alcohol misuse and provide persons engaged in risky or hazardous drinking with brief behavioral counseling to reduce alcohol misuse; this is a B recommendation; the brief behavioral intervention is referred to as SBIRT (Screening, Brief Intervention, and Referral to Treatment); for tobacco use screening, it is recommended that clinicians ask all adults who are not pregnant about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and US FDA-approved pharmacotherapy for cessation to adults who use tobacco; this is a grade A recommendation

Cancer screening — prostate: the PSA screening guidelines changed in April from a D to a C; age-appropriate screening with shared decision-making between the physician and the patient is now included in the Task Force guidelines for men between the ages of 55 and 69; the Task Force recommends not screening men over the age of 70; I would make an exception to this for black men because they are at a higher risk of prostate cancer; you will receive requests for screening from black patients in your practice who are younger than 55; be prepared to offer them screening with shared decision-making; this is a level C guideline; there is evidence to support this in the literature

Cancer screening — lung: low-dose CT (LDCT)screening has a B recommendation for patients between the ages of 55 and 80 who have a 30-pack-year smoking history and who currently smoke or have quit within the last 15 years; screenings should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery; this is a more complex guideline for use of the ultra-fine CT for lung cancer screening

Cancer screening — colorectal: a grade A recommendation for ages 50 to 75; the risks and benefits vary among the different technologies, but it is basically fecal immunochemical testing such as Cologuard; the decision to screen for colorectal cancer in adults aged 76 to 85 is an individual one, taking into account the patient's overall health and prior screening history, so it could be considered a C recommendation in that age group; has an A recommendation for ages 50 to 55

Cancer screening — breast: the Task Force recommends biennial screening mammography for women aged 50 to 74, and that is a B recommendation; the decision to start screening mammograms in women prior to 50 is an individual one, that once again involves shared decision-making; it can be biennial has a C recommendation between the ages of 40 and 49, as it has the potential to do more harm than good or the reverse, depending on the individual's family history, etc.

Cancer screening — cervical: it is recommended that screening be performed with cytology for cervical cancer in women aged 21 to 65, including the pap smear every 3 years; or, for women aged 30 to 65 who wish to lengthen the screening interval, the combination of cytology and HPV testing can be done every 5 years; that is a grade A recommendation

Genetic testing

BRCA testing: issue of genetic testing often comes up in context of BRCA tests for breast, ovarian, tubal, or peritoneal cancer, particularly in women with positive family history for one of these cancers; screening for potentially harmful mutations in breast cancer susceptibility genes with several types of genetic tests is recommended for women with family members with breast, ovarian, tubal or peritoneal cancer; women with positive results should receive genetic counselling and BRCA testing if indicated; of note is that 5% of men at risk for prostate cancer are affected by BRCA mutations; these BRCA testing recommendations have a B rating;

Genetic testing — general considerations: information is from NIH (National Institutes of Health) websites relating to genetic testing and genetic testing for hereditary cancers; patients should provide their primary care physician with a good family history whether genetic testing is discussed or not; it is an essential component of the health assessment; often, the subject of genetic testing is brought up by the patient because of concerns relating to diseases in relatives and concerns about the patient's children or planned future children; genetic testing is helpful in determining whether family members without obvious illness have inherited the same mutation as a family member who is known to be a carrier of an associated mutation; adoptions are a common area where the patient will want to discuss genetic testing; genetic testing may be discussed because the patient is adopted and is requesting testing for him- or herself, or because the patient has adopted a child from the US or abroad; complete medical history of the child or the child's parents is notoriously absent in the latter case; if available, it may not be reliable

Predictive testing: note that "genetic testing" is a broad term encompassing several types of testing; predictive or presymptomatic tests are used to detect gene mutations

associated with disorders that appear postnatally, often later in life;hey could be incomplete penetrants, different levels of gene expression; this type of testing can be helpful to patients who have a family member with a genetic disorder but have no manifestations of the disorder themselves; an example is hereditary hemochromatosis, one of the Low Value Care items; we don't really recommend screening for this

Benefits of predictive testing: genetic testing has a potential benefit whether the results are positive or negative for gene mutation; test results can provide a sense of relief from uncertainty and help people make informed decisions about managing their health care; some test results can help people make decisions about having children; it can connect the patient with the right specialist; it can also help determine the need for screening or surveillance

Risks and limitations: there can be adverse emotional, social, or financial consequences of test results, such as endless work-ups; in some cases, genetic testing increases tension within a family; an unequivocal diagnosis won't necessarily impact a treatment plan; there can be a negative psychological impact in the form of worry about the future, the chance of passing the condition to offspring, or the risk for other relatives; there is also a tremendous amount of uncertainty in genetic testing, so that often the patient will not get a simple answer about the cause of their condition;

Requests: when a patient requests genetic testing, you should be prepared to either order or manage the testing yourself or refer the patient to a practice with which you are familiar; get to know the referral options that you have within your system; it is not unusual for a patient to present with a stack of genetic test reports from tests they have ordered themselves and request your interpretation; the same practical concern applies in both scenarios; in both cases, the obvious consideration is determining what aspects of genetic testing are covered under the patient's healthcare plan

Common diagnostic tests: BRCA1 and BRCA2 (these apply to prostate cancer as well as breast and ovarian cancers); Lynch Syndrome (hereditary nonpolyposis colorectal cancer); related cancer types such as colorectal cancer and many others; non-cancer related conditions include Huntington's Disease and post-onset familial Alzheimer's disease

Pharmacogenetic testing: also called drug gene testing or pharmacogenomics, it is the study of how a person's genes affect the way he or she metabolizes medications; when patients are having unusual metabolism of drugs, it may be useful to pursue pharmacogenetic testing; genetic conditions can affect toxicity and drug interactions; psychotherapeutic agents and oncology medications are two examples where this occurs with some degree of regularity; some of the currently available pharmacogenetic tests include CYP2C19 testing, which is used to determine a potential risk for side effects of antidepressants like citalopram; CYP2C19 tests are also used to predict how a patient will respond to clopidogrel

Genetic counseling: a geneticist or genetic counselor provides information about the pros and cons of tests in question, and discusses the social and emotional aspects of testing with the patient; the counselor can help the individual or family to understand the test results; counseling may include discussing the recommendations for preventive care and screening of the patient, referring the patient to support groups, and providing other information, resources, or emotional support to the persons receiving the results

Immunizations in adults

General considerations: lecturer stresses: providing age- and risk-based immunizations is the most cost-effective preventive health intervention available; please consult the CDC (Centers for Disease Control)and the Advisory Committee on Immunization Practices (ACIP) for complete vaccination schedules and specific adult age bases for these vaccinations; schedules vary with the different immunizations depending on the patient's age and previous vaccination history; universal vaccine contraindications (common to all vaccines) — a severe anaphylactic reaction or allergic reaction; on a previous dose, a specific-component reaction

Influenza: the most common types of flu vaccine are the recombinant and cell-based vaccines; everyone 6 months of age and older is recommended to have an annual flu vaccine except for those falling under the universal vaccine contraindications

Pneumococcal disease: can affect adults; ranges from otitis media, meningitis, and pneumonia to bacteremia; adults 65 years of age and older are those who are at most risk of this disease; the CDC recommends pneumococcal vaccine with PCV13 or PSV23 for all adults 65 and older; the contraindications are the universal ones mentioned previously

Shingles (herpes zoster): the most common complication is postherpetic neuralgia (PHN); the CDC recommends Shingrix as the preferred vaccine over Zostavax, which is a shingles vaccine that has been in use since 2006; a patient should get Shingrix even if they previously had shingles, received Zostavax, or are not sure whether they had chicken pox; Shingrix reduces the risk of shingles and postherpetic neuralgia by more than 90% in people aged 50 or older; there is no maximum age for getting Shingrix; contraindications include a weakened immune system due to HIV, cancer treatment, radiation, chemotherapy, or bone marrow lymphatic cancers such as leukemia or lymphoma; women who might be pregnant should not become pregnant until at least 4 weeks after receiving zoster vaccine

Tetanus and pertussis: CDC recommends a single dose of Tdap for adults ≥19 years who have not previously received Tdap; being up to date with one dose of Tdap is especially important for adults who are around babies as caregivers; even fully immunized adults can get pertussis and pass it to infants who are not immunized; contraindications include encephalopathy not attributable to identifiable causes within 7 days of administration of DTP, DTaP, or Tdap;

HPV: almost everyone is infected at some point in their lives, and they may be asymptomatic; HPV vaccine is recommended for young women through the ages of 26, and young men through the ages of 21; HPV vaccine is also recommended for the following individuals if they were not vaccinated when they were younger: young men who have sex with men, including young men who identify as gay or bisexual and young men who are transgender through age 26, and young adults with certain

immunocompromising conditions, including HIV, through age 26; contraindications include anaphylactic allergy to latex, and, in patients with a history of immediate hypersensitivity to yeast, quadrivalent and 9-valent HPV vaccines (produced in baker's yeast)

Measles, mumps, and rubella (MMR): adults who lack evidence of immunity (ie, written documentation of adequate immunization, laboratory evidence of immunity, laboratory confirmation of measles, or birth before 1957) should receive MMR; healthcare personnel who do not have documented evidence of immunity should be vaccinated according to the schedule; contraindications include known severe immunodeficiency, hematological and solid tumors, chemotherapy, congenital immunodeficiency syndromes, long-term immunosuppressive therapy, whether it be medication for transplant or long-term steroid use, and pregnancy; other contraindications include family history of congenital or hereditary immunodeficiency in first-degree relatives, unless the competence of the potential vaccine recipient has been substantiated clinically by a verified laboratory test

Meningococcal disease: 2 types of meningococcal vaccine — meningococcal conjugate vaccine and serogroup B meningococcal vaccine; adults 19 years of age and older who will need both meningococcal conjugate and serogroup B vaccines are individuals who have severe complement component deficiencies or are taking Soliris (eculizumab), or who have functional or anatomic asplenia such as with sicklers, or microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*; unique indications include travelers to or residents in a country in which the disease is common, being part of a population identified to be at increased risk (serogroup A, C, W, Y) and a meningococcal disease outbreak, first-year college students living in a residence hall, military recruits; additional unique indications for serogroup B vaccine conjugate include being part of a population known to be at increased risk of serogroup B meningococcal disease outbreak; universal vaccine contraindications only

Hepatitis A/B: adult indications for HAV and HBV vaccines are travel to or residence in a country where the diseases are epidemic, men having sex with men, injection drug use, people at an occupational risk of exposure, those with chronic liver disease, people who have direct contact with HAV or HBV; consult the CDC and ACIP for specifics of both Hepatitis A and Hepatitis B vaccination; Hepatitis A vaccine is not routinely recommended for healthcare personnel, sewage workers, daycare workers, or food service workers; universal vaccine contraindications only

Key points: 1) Get with the guidelines — we want to use the screening recommendations from the USPSTF as a benchmark, and these are constantly being updated; 2) we want to use the High Value Care statements and we want to avoid doing tests that don't add value; 3) build trust with the patient and use the periodic health exam to engage in lifestyle medicine discussions after you build trust

Question to consider #1: a patient comes in and says they are adopted and they want to talk with you about genetic testing; what do you tell them? A, it's not indicated; B, you listen to their concerns and offer them a referral for genetic testing and counseling; C, none of the above; the best answer would be that you listen to the concerns and offer them the ability to follow up and have some genetic testing and counseling if that is their desire; otherwise, you will not satisfy this particular patient

Question to consider #2: a 45-year-old black man is requesting a PSA test; you've read the most recent set of guidelines for PSA testing according to the USPSTF, and you're in a quandary how to apply this to this patient; what do you do? A, defer until he's age 50; B, go forward with the testing because he's requesting it; C, none of the above; I believe the correct answer is B, go forward with it; he is requesting it; it's a shared decision-making process; you can make a case for a grade C recommendation; there is evidence in the literature to support testing even though the patient is younger than the recommended age of 55 years for starting testing; black men are at a higher risk than others for prostate cancer

Question to consider #3: a 45-year-old woman is requesting a mammogram from you; What do you do? A, tell her it is not indicated; B, offer it based on her individual decision and your decision; C, offer it based on a grade B recommendation of the Task Force; it's not a grade B recommendation, so C is incorrect; it is a grade C recommendation according to the Task Force; you can offer it; it's individual decision-making, shared decision-making, so the correct answer is B; women who place a high value on the potential benefit versus the harms may begin biennial screening between the ages of 40 and 49

Suggested Reading

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Medical Care of the Pregnant Patient

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Pregnancy in women aged >40 yrs: rates have increased dramatically; in 2017, Centers for Disease Control and Prevention (CDC) report showed that pregnancy rates static or declining in all age groups except women aged 40 to 44 yrs; important because increased likelihood that we will be treating women with preexisting medical problems that may be exacerbated by pregnancy or presence of those conditions during pregnancy makes them more likely to come into contact with internists

Underlying chronic disease: pregnancy likely to unmask occult chronic diseases such as glucose intolerance, renal dysfunction, hypercoagulable states, valvular heart diseases, cerebral aneurysm; some have referred to pregnancy as "stress test for life"; increased rates of postpartum chronic disease; women with gestational diabetes, 75% increased likelihood of developing type 2 diabetes in next 5 yrs; preeclampsia, more likely to develop coronary artery disease and stroke later in life (higher rates of hypertension (HTN), insulin resistance, dyslipidemia, inflammatory markers); primary prevention important

Primary care providers need to understand medical illness and its management in pregnancy: includes contraception, preconception counseling, patient education; collaboration with subspecialists (*eg*, maternal-fetal medicine); understand physiologic changes of pregnancy and how they affect disease; basic knowledge of pregnancy-specific illnesses; strategy for evaluating drug safety

Asthma

Overview: most common chronic medical illness to complicate pregnancy; affects up to 3% to 8% of women of childbearing age; often underdiagnosed or undertreated; significant increase in complications of pregnancy; largest study to date showed 15% to 20% increase in risk of perinatal mortality, preeclampsia, preterm delivery, or low birth weight compared with nonasthmatic women; patients with severe asthma have 30% to 100% increased risk

Case 1: 23-yr-old nonsmoking woman, gravida 1, para 0; 11 wks gestation; 8-year history of asthma, worsened over past 1 yr; requires albuterol 2 to 3 times per day; interferes with sleep every night; forced expiratory volume in 1 sec (FEV_1) 65% of predicted value, increases to 88% percent after albuterol; *how to manage?* — A. continue current regimen; B. add budesonide; C. add theophylline; D. add salmeterol; E. add inhaled cromolyn

Physiology of respiratory changes in pregnancy: increased O_2 demand, with 20% increase in O_2 consumption; tidal volume increases; small increase in respiratory rate causes large changes in minute ventilation; slight heart rate (HR) increase causes 40% to 50% increase in minute ventilation; increased inspiratory capacity; deceased residual volume and expiratory reserve decreases; marked reduction in functional residual capacity from diaphragmatic elevation and increased subcostal angle and transverse thoracic diameter; FEV_1 and peak expiratory flow rate unchanged; progesterone likely changes ventilation and reduces CO_2 through direct action on respiratory center; increased carbonic anhydrase in maternal red cells leads to increased breakdown of CO_2 and excretion of bicarbonate through maternal kidneys; functional changes facilitate air flow along bronchial tree; women with chronic respiratory disease tend to deteriorate less in pregnancy; peak expiratory flow and FEV_1 can still be valid in pregnant asthmatic women; shortness of breath (SOB) common in pregnancy, so can complicate assessment; individual variations in chemoreceptors and physiologic increase in blood shunted away from functional alveoli

Case 1 (continued): *how to manage?* — emphasis on prevention, rather than treatment; no different than that for nonpregnant women; optimize control prior to pregnancy and achieve control as soon as possible for patient with new diagnosis; beta-2 agonists plus or minus inhaled corticosteroids mainstay of treatment

Medications: beta-2 agonists safe in pregnancy; experience with newer agents growing (appear safe); no adverse fetal effects with inhaled disodium cromoglycate, nedocromil, anticholinergics (*eg*, ipratropium), or inhaled corticosteroids; with inhaled steroids, minimal absorption and no evidence of fetal malformations or adverse fetal effects; do not withhold oral steroids or systemic steroids in acute attacks; no strong evidence of fetal malformations, miscarriage, stillbirth, or neonatal death; steroids worsen glycemic control in diabetic patients; long-term steroid use may increase risk of gestational diabetes; long-term high-dose steroids lead to increased risk of premature rupture of membranes; when patient presents with acute asthma attack, manage as if nonpregnant, with intravenous (IV) rehydration, O_2, beta-2 agonist, O_2 nebulizer; chest x-ray if suspicion of pneumothorax, pneumonia, or failure to improve after initial treatment; steroids given just as if patient not pregnant (some believe often inappropriately withheld); if patient not improving, may need IV steroids or inhaled beta-2 agonists plus or minus magnesium sulfate; if level 4 asthma (need immune modulators), refer to high-risk obstetrics specialist

Seizures

Case 2: 25-year-old woman with epilepsy; seeking advice about pregnancy; first developed seizures after head injury in motor vehicle collision at age 16 yrs; magnetic resonance imaging (MRI) studies since then have shown area of encephalomalacia in right temporal lobe; seizures initially refractory to carbamazepine and valproic acid monotherapy; carbamazepine stopped and lamotrigine added to valproic acid 1 yr ago; no seizures since that time; *how to manage most appropriately?* — A. advise patient not to become pregnant; B. continue valproic acid and lamotrigine; C. discontinue valproic acid and continue lamotrigine; D. discontinue valproic acid and lamotrigine; E. substitute phenobarbital for current medications

Overview: ~0.5% of women of childbearing age have epilepsy, most known prior to pregnancy; all seizure types may be affected by pregnancy; associated with risk of maternal death from aspiration and sudden unexplained death

Effects of pregnancy: 25% to 30% increase in seizure frequency; no change in 54%; if seizure free, unlikely to have seizures during pregnancy unless stop medication; if poorly controlled >1 mo, likely to deteriorate in pregnancy; high risk in peripartum period

Reasons for deterioration: pregnancy itself; poor compliance because of fears of teratogenesis; decreased drug levels from nausea and vomiting and increased volume distribution and drug clearance; lack of sleep toward term and during labor; lack of absorption of drugs or hyperventilation during labor

Effects of epilepsy on pregnancy: fetus relatively resistant to short-term hypoxia (*eg*, during seizures); no evidence of adverse effects on fetus; no increased risk of miscarriage or obstetric complications (*eg*, intrauterine growth retardation); status epilepticus in <1% but dangerous for mother and baby, so treat vigorously; major risk, teratogenicity from drugs, but even women not on treatment have increased risk of malformations (4%, vs 3% in general population); risk of child developing epilepsy depends on who has epilepsy (5% risk if either parent has epilepsy, 15%- 20% if both parents have epilepsy, 10% if sibling has epilepsy, 9%- 12% if parent has idiopathic generalized seizures, 3% if parent has partial seizures)

Teratogenic risks of anticonvulsants: newer drugs once thought to be safe now show risks with use; *major malformations* — neural tube defects, especially with valproate (1%- 2%) and carbamazepine (0.5%- 1%); orofacial clefts, especially with phenytoin; cardiac defects, especially with phenytoin and valproate; minor malformations (fetal anticonvulsant syndrome) characterized by dysmorphic features (V-shaped eye brows, low-set ears, broad nasal bridge, and irregular teeth), hypertelorism, hypoplastic nails in distal digits; little difference in risk level among drugs; 6% to 7% risk with any 1 drug; risk increases with number of drugs; 2 or more drugs, 15%; phenytoin plus valproate plus carbamazepine, 50%; benzodiazepines not teratogenic; mechanism likely folate deficiency; all women should take folate (5 mg/day) prior to conception and throughout pregnancy

Management: advise patients to take folic acid 5 mg/day from ≥12 weeks prior to conception, continue throughout pregnancy; continue current drugs if seizures well controlled, except wean off or change phenobarbital due to risk of neonatal withdrawal seizures; detailed fetal scan at 18 wks to 20 wks; detailed fetal cardiac scan at 22 wks; advise shallow baths or shower because of risk of drowning if seizure while in tub; advise relatives regarding recovery position for seizures; if steroids given, increase dose if enzyme-inducing drugs (*eg*, phenytoin, phenobarbital, or carbamazepine) being used; when administering vitamin K, give higher dose from 34 wks to 36 wks if on enzyme inducers, to prevent fetal vitamin K deficiency and hemorrhagic disease of newborn

Cardiovascular (CV) Issues

Case 3: African American woman aged 35 yrs; progressive SOB 3 wks after delivery of first child; uncomplicated pregnancy and delivery except for HTN; no history of CV disease (CVD); blood pressure (BP) 110/70 mm Hg in both upper extremities; HR 105 bpm, regular; respiratory rate 28 breaths/minute; estimated central venous pressure (CVP) high (10 cm H_2O); no carotid bruits; apical impulse displaced and diffuse; grade 2/6 holosystolic murmur noted at apex; third and fourth heart sounds noted at apex; dullness to percussion in posterior lung bases bilaterally; crackles extending halfway up lung fields; lower extremity pulses normal and without delay; pedal edema; electrocardiogram (ECG) shows sinus tachycardia, no ST segment or T-wave changes; chest radiograph shows bilateral pleural effusions and interstitial infiltrates, unremarkable aortic contour; *most likely cause?* — A. acute myocardial infarction; B. aortic dissection; C. aortic coarctation; D. acute pulmonary embolism; E. peripartum cardiomyopathy

Peripartum cardiomyopathy: heart failure with ejection fraction (EF) <45%; diagnosed from 3 mos before delivery to 6 mos postpartum (usually within 1 mo postpartum) in absence of identifiable cause; *typical features* — time of onset, evidence of left ventricular (LV) dilation, displaced and diffuse apical impulse, and typical signs of heart failure (HF); main risk factors include age ≥ 30 yrs, African American or Haitian ethnicity, and gestational HTN; maternal mortality 10% (major cause of pregnancy-related death in North America); urgent confirmation of global ventricular systolic dysfunction by transthoracic echocardiogram; treatment with standard HF therapy; often, improvement in LV function in 50% of women within 6 months of delivery; IV immunoglobulin and pentoxifylline may improve outcomes; anticoagulation recommended for thromboembolic prophylaxis when EF <35%

CV physiologic changes during pregnancy: blood volume and cardiac output increase by 50% (half of this occurs by week 8 of pregnancy); maximum blood volume expansion at 28 weeks; labor may increase cardiac output another 50%; 10% to 20% increase in HR; 25% decrease in systemic vascular resistance; systolic BP tends to decrease by 5 mm Hg to 10 mm Hg diastolic BP by 10 mm Hg to 15 mm Hg; oncotic pressure changes; 50% increase in plasma volume and 33% increase in red cell mass, with resulting dilutional anemia

Predictors of poor outcome in heart disease during pregnancy: New York Heart Association Class III or IV (symptoms with less than ordinary physical activity or at

rest); history of prior cardiac event or arrhythmia; left-sided obstruction in mitral or aortic valve, EF <40%

Case 4: woman aged 26 yrs; 25 wks pregnant; evaluated in emergency department for palpitations and episodic lightheadedness; no history of CVD or tachycardia; BP 100/70 mm Hg; HR 175 bpm; estimated CVP normal; no carotid bruits; apical impulse not displaced; no murmurs or abnormal heart sounds; exam otherwise unremarkable; Valsalva maneuver and carotid sinus massage does not affect tachycardia; ECG shows regular narrow-complex tachycardia; *most appropriate IV medication to administer?* — A. adenosine; B. amiodarone; C. digoxin; D. diltiazem; E. metoprolol

Case 5: woman aged 29 yrs; prepregnancy mechanical mitral valve prothesis; presents for prepregnancy counseling; history of mitral regurgitation with mitral valve replacement for progressive LV enlargement several yrs ago; recently married and would like to have family; asymptomatic; stable dose of warfarin 4 mg/day for last 2 yrs; BP 120/70 mm Hg; estimated CVP 3 cm H_2O; crisp mechanical S1; no murmurs; remainder of exam unremarkable; *what anticoagulation regimen should be used for mechanical prosthetic valves in this patient if she decides to become pregnant?* — A. continue warfarin and adjust to international normalized ration (INR); B. stop warfarin and start aspirin and clopidogrel; C. stop warfarin, start fondaparinux; D. stop warfarin, start weight-based low-molecular-weight (LMW) heparin; E. stop warfarin and start dabigatran

Warfarin: low molecular weight; crosses placenta, causes poor fetal outcomes (especially in first trimester); causes embryopathy, stillbirth, intracranial hemorrhage, and spontaneous abortion; but lowest risk for maternal complications and death; used outside of US

LMW heparins: approved for deep vein thrombosis and pulmonary embolus (PE) but not anticoagulation for mechanical valves; best choice in this case; weight-based dosing inadequate; need to monitor anti-factor Xa activity levels weekly or biweekly to guide dosing

Prescribing in pregnancy: do not start medication unless clearly indicated; do not discontinue medicines that successfully maintain maternal condition unless clear indications to do so; ask about undocumented and nonprescription medications; have pregnancy medication reference available; favor older medications with longer record of use; check blood levels and consider increased and/or more frequent dosing because of increase in volume of distribution, hepatic and renal clearance, and increased production of binding proteins; free drug levels better; educate and negotiate, because pregnant women more likely to stop needed medications because they do not want to harm baby; report adverse outcomes; consider effect of not treating; few drugs absolutely contraindicated

FDA drug ratings in pregnancy: categories A, B, C, D, and X; A, controlled human studies show no risk; B, no evidence of risk in studies; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated; many of medications either C or D; can be hard to remember and may be misleading because ≤60% of category X drugs have no human data or information on degree of risk; drug may end up in category X simply if no utility in pregnancy; FDA classification rarely updated

Contraindicated drugs during pregnancy: angiotensin-converting enzyme (ACE) inhibitors (renal dysgenesis); tetracycline (bone and teeth abnormalities); fluoroquinolones (abnormal cartilage development); systemic retinoids (central nervous system [CNS], craniofacial, and CV defects); warfarin (skeletal and CNS defects); valproic acid (neural tube defects); nonsteroidal anti-inflammatory drugs (bleeding, premature closing of ductus arteriosus); live vaccines (MMR, oral polio, varicella, yellow fever) because may cross placenta

Drug prescribing references: Reprotox (www.reprotox.org; paid subscription); Mother Risk (www.motherrisk.org); Micromedics; Organization of Teratology Information Specialists (OTIS; MotherToBaby; mothertobaby.org), free and useful but requires registration; ibreastfeeding.com (Medications and Mother's Milk Online; medsmilk.org)

Reprotox summary for citalopram: based on experimental animal studies and limited human reports, standard therapeutic use of citalopram not expected to increase risk of congenital anomalies; use of serotonin reuptake inhibitors late in pregnancy can be associated with mild transient neonatal syndrome of CNS, motor, respiratory, and gastrointestinal (GI) signs; in small number of cases, use of other serotonin reuptake inhibitors after 20 wks gestation associated with increased risk neonatal pulmonary HTN

Case 6: woman aged 39 yrs; gravida 4, para 2; new primary care appointment; obese; history of PE in prior pregnancy; urine pregnancy test positive; 9 wks pregnant by last menstrual period; mild SOB; O_2 saturation 93%; *changes in respiratory and hematologic systems in pregnancy and how would they affect patient?*

Pulmonary physiologic changes: increase in minute ventilation mediated by progesterone; increase in tidal volume ≥ increase in respiratory rate; compensated respiratory alkalosis; normal arterial blood gas (pH 7.43, partial pressure of carbon dioxide [P_{CO_2}] 29, partial pressure of O_2 [P_{O_2}] 100); P_{CO_2} of 40 very abnormal in pregnancy; fetus relies on high maternal partial arterial pressure of O_2 [Pa_{O_2}]; greater tendency for pulmonary edema with increased cardiac output, decreased oncotic pressure, leaky capillaries; medications used and aggressive fluid hydration can compound this

Hematologic changes: increase in procoagulant factors (factor VIII, von Willebrand factor, fibrinogen); protein S levels markedly reduced; increased risk of venous clots (most pronounced in postpartum period)

Endocrine system changes: increase in insulin resistance; dyslipidemia; relative suppression of thyroid-stimulating hormone in first trimester; other changes in thyroid function

Renal changes: increased glomerular filtration rate, which increases baseline proteinuria; drugs more rapidly metabolized by kidney; creatinine falls; collecting system dilates

Case 6 (continued): order chest x-ray for initial evaluation, but concerned about x-ray effects on fetus; *what would you say?*

Principles of diagnostic imaging: if greater risk of harm by not getting needed study than by getting one, get study; little evidence that radiation exposures <5 rad have

significant fetal effects; almost all imaging studies involve radiation well below this level; chest x-rays <.001 rad; computed tomography (CT) protocol,.001 rad to.002 rad; CT abdomen and pelvis,.64 rad; theoretical concern for IV contrast and potential impact on fetal thyroid; case reports of women receiving high-dose iodine in pregnancy but no adverse fetal outcomes; avoid if possible but use contrast when clinically necessary; few studies with MRIs, but animal evidence shows little risk; National Institutes of Health (NIH) consensus statement recommends MRI be reserved for second and third trimesters, but can be performed in pregnancy and gadolinium used if indicated, though use caution, because little data exist

Case 6 (continued): patient had CT showing PE; managed with treatment-dose LMW heparin, converted to subcutaneous unfractionated heparin at 36 wks; vaginal delivery of healthy baby boy

Liver Problems

Case 7: woman age 23 yrs; intractable itching; gravida 2, para 1; 35 wks with singleton gestation; referred from dermatologist for intractable itching, primarily on palms of hands and soles of feet; present day and night and keeps her from sleeping; itching during her first pregnancy, in which fetus died in utero in third trimester; no explanation given for fetal demise and previous pregnancy was otherwise uncomplicated; autopsy and karyotype of fetus were normal; no known prior history of liver disease or risk of viral hepatitis; physical exam notable for numerous skin excoriations related to scratching, gravid uterus; no abdominal pain; nonpalpable liver or spleen; lab evaluation notable for elevation of serum aminotransferases, alkaline phosphatase, and total bilirubin; alanine aminotransferase (ALT) 1201 IU/L; aspartate transaminase (AST) 910 IU/L; bilirubin 3.1 mg/dL; alkaline phosphatase (ALP) 400 IU/L; gamma-glutamyl transpeptidase (GGTP) normal; total serum bile acid concentration 10 times normal; viral hepatitis serologies negative; right upper-quadrant ultrasound normal; *diagnosis?* — A. acute viral hepatitis; B. choledocholithiasis; C. primary biliary cirrhosis; D. cholangitis; E. intrahepatic cholestasis of pregnancy

Clinical presentation: consistent with intrahepatic cholestasis of pregnancy; serologic testing excluded viral hepatitis; very high levels of aminotransferases with normal GGTP, making primary biliary cirrhosis unlikely; absence of abdominal pain, fever, or biliary duct dilatation helps exclude choledocholithiasis and cholangitis; prior history of itching during pregnancy helpful, since intrahepatic cholestasis of pregnancy tends to recur; intrauterine demise during prior pregnancy may reflect adverse fetal outcomes associated with this condition and should prompt increased fetal monitoring with consideration for early delivery; ursodeoxycholic acid (UDCA) increases bile flow and has been used to relieve pruritus and improve liver biochemical tests in patients with intrahepatic cholestasis of pregnancy; no adverse effects on mothers or babies reported; pooled analysis comparing UDCA with controls showed improvement in pruritus (61% vs 27%), total resolution of pruritus (42% vs 6%), improvements in transaminase and serum bile acid concentrations, and lower premature delivery rate (16% vs 34%; odds ratio, 0.44)

Case 8: woman aged 24 yrs; elevated aminotransferases; gravida 3, para 2; 14th wk, singleton gestation; hospitalized with intractable nausea, vomiting, and dehydration; during her 2 prior pregnancies, she also had severe nausea and vomiting that resolved early in second trimester; past medical history otherwise unremarkable; no travel in past 1 yr; only medications prenatal vitamins and folate; dry mucous membranes, gravid uterus; no abdominal pain; no palpable liver or spleen; elevations in serum aminotransferases; ALT 175 IU/L; AST 122 IU/L; serum total bilirubin 2.1 mg/dL; amylase and lipase normal; albumin slightly increased from normal levels but consistent with pregnancy; liver biochemical tests prior to pregnancy not available; right upper-quadrant ultrasound normal; urinalysis shows elevated ketones; *diagnosis?* — A. viral hepatitis; B. autoimmune hepatitis; C. drug toxicity; D., hyperemesis gravidarum

Additional testing: hepatitis A, B, and C serologies negative; antinuclear antibodies absent; serum protein electrophoresis normal (making autoimmune hepatitis unlikely); TSH normal; obstetric ultrasound exam demonstrates normal singleton gestation

Treatment: antiemetics, IV fluids; at 20 wks gestation, symptoms completely abated and liver biochemical tests returned to normal

Case 9: woman aged 23 yrs; elevated aminotransferases; para 1, gravida 0 with twin gestation at 30 wks; hospitalized with HTN; methyldopa prescribed at 28 wks gestation; despite treatment, she continues to be mildly hypertensive and serum aminotransferases progressively rising (>85 IU/L); hepatitis serology markers for immune hepatitis negative; platelet count, peripheral blood smear, right upper quadrant ultrasound normal; urinalysis normal except 1+ proteinuria; within 36 hrs, she develops progressive thrombocytopenia, worsening HTN, headache, and serum aminotransferases rise further; *diagnosis?* — A. toxicity due to methyldopa; B. early acute fatty liver of pregnancy; C. severe preeclampsia; D. autoimmune hepatitis; E. hyperemesis gravidarum

Case 10: woman aged 32 yrs; gravida 1, para 0, singleton gestation; 34 wks gestation; admitted to hospital; 3-day history of nausea and vomiting, malaise, and jaundice; BP mildly elevated; urinalysis show trace protein; serum aminotransferases, range from 200 IU/L to 500 IU/L; glucose lower-normal range; white blood cell count and prothrombin time elevated; denies recent travel; hepatitis serologies sent but unavailable; *diagnosis?* — A. acute fatty liver of pregnancy; B. hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome; C. atypical preeclampsia; D. viral hepatitis; E. intrahepatic cholestasis of pregnancy

Liver disease in pregnancy:

Hyperemesis gravidarum: expect in first and early second trimester; aminotransferases <200 IU/L; ALT usually ≥ AST (rarely, as high as 1000 IU/L); total bilirubin <4 mg/dL; differential diagnosis includes gastroenteritis, cholecystitis, hepatitis, intestinal obstruction, peptic ulcer disease, pancreatitis, appendicitis, diabetic ketoacidosis, hyperparathyroidism, hyperthyroidism, and drug toxicity; maternal and fetal mortality rare; disease can recur in other pregnancies

HELLP syndrome: occurs in later part of second trimester through delivery; aminotransaminase levels <500 IU/L (median 250 IU/L unless hepatic infarction); median

total bilirubin 1.5 mg/dL; platelets <100,000; lactate dehydrogenase (LDH) >600; differential diagnosis includes acute fatty liver of pregnancy, gastroenteritis, hepatitis, pyelonephritis, appendicitis, cholelithiasis, idiopathic thrombocytopenia purpura, and hemolytic uremic syndrome; maternal mortality low, complications high; fetal mortality may be as high as 35%; can recur in other pregnancies (3%-27%)

Intrahepatic cholestasis: occurs in third trimester until delivery; AST usually <500 IU/L but can be >1000 IU/L; total bilirubin <6; bile acids increased; ALP increased up to 4 times normal, out of proportion to GGTP; differential diagnosis includes cholelithiasis, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and drug hepatotoxicity; maternal mortality rare; fetal mortality 1% to 2%; associated with prematurity and stillbirth; recurs in 60% to 70% of subsequent pregnancies

Acute fatty liver of pregnancy: occurs in same distribution as intrahepatic cholestasis; third trimester to delivery; AST <500 IU/L but may be as high as 1000 IU/L; bilirubin elevated; leukocytosis; elevated prothrombin time; platelets low; hypoglycemia; hyperuricemia; differential diagnosis includes HELLP syndrome, drug toxicity, and fulminant hepatic failure; maternal mortality <3%; fetal mortality as high as 35% to 45%; recurrence rare

Incidence of liver disease in pregnancy: ≤3% of deliveries associated with abnormal liver tests; most cases attributable to pregnancy-specific disorders (*eg*, preeclampsia, HELLP syndrome, obstetric cholestasis, hyperemesis, and acute fatty liver of pregnancy); others result from sepsis, drug-related causes, bile-duct stones, hepatitis, or uncertain etiology

Liver tests in normal pregnancy: increased or decreased in relation to values in nonpregnant women; albumin and total protein decreased from first trimester onward; ALP increased in second and third trimesters; bilirubin levels slightly decreased from first trimester; GGTP levels slightly decreased in late pregnancy; ALT, AST, prothrombin time, LDH, and serum concentration of total bile acids in fasting state unaffected by pregnancy

Liver disease evaluation in pregnancy: ask about pruritus during previous pregnancies or while on oral contraceptives; ask about abdominal pain, nausea or vomiting, polyuria, polydipsia, drugs or drug exposure, exposure to viral hepatitis, prior history of gallstones; note trimester of pregnancy; assess temperature, BP; look for proteinuria; examine liver carefully; check complete blood count with platelets, routine liver function tests (LFTs) including prothrombin time; serum creatinine, electrolytes, glucose, uric acid levels; serologies (viral hepatitis A, B, and C and cytomegalovirus, hepatitis E if suspicion); measure total serum bile acids if cholestasis suspected; urinalysis and culture; ultrasound of liver and bile ducts; monitor evolution of symptoms and LFTs before and after delivery

Depression

Question from physician: "one of my patients who was taking an antidepressant for major depression is now pregnant and does not wish to take it anymore; I believe she needs to continue her medication; however, she is adamant about stopping it because she believes it would put her baby at risk; is there evidence that not treating depression during pregnancy puts babies at risk?"

Effects of depression on mother and baby: untreated depression associated with adverse fetal outcomes and higher risk of maternal morbidity (*eg*, suicidal ideation, suicide attempts, postpartum depression); untreated depression during pregnancy linked to adverse outcomes (*eg*, spontaneous abortion, increased uterine artery resistance, small head circumference of baby, low Apgar scores, need for special neonatal care, neonatal growth retardation, preterm delivery, babies with high cortisol levels at birth); studies suggest that pregnant women with depression require more operative deliveries and report more painful labor (*ie*, require more epidural analgesia); gestational HTN and subsequent preeclampsia linked to untreated depression during pregnancy; psychopathology during pregnancy thought to affect uterine environment and could affect fetal outcome; women with untreated antenatal depression at increased risk of postpartum depression; less capable of carrying out maternal duties and bonding with their babies; 1 study found elevated risk of preterm delivery (<37 wks), low birth weight (<2500 g), and small-for-gestational-age (<10th percentile) babies of women with Beck Depression Inventory score of ≥21 not receiving treatment; prenatal stress and depression associated with lower infant birth weight and younger gestational age at birth (confirmed by recent study that investigated link between depression and preeclampsia)

Classes of medication for treating women who have depression during pregnancy: depends on whether or not they have had prior exposure to any treatment, if they have medications that have proven effective, and whether or not they have other comorbid psychiatric diagnoses; for unipolar depression, selective serotonin reuptake inhibitors (SSRIs) preferred; among SSRIs, sertraline favored if no previous antidepressant use; citalopram and escitalopram reasonable alternatives; observational study evidence that first-trimester exposure to these 3 medications associated with little or no risk of teratogenicity; other observational studies found sertraline reasonable during lactation; if other medications have been useful, patient should continue them; consider coexisting or comorbid psychiatric diagnoses

Suggested Reading

MotherToBaby: Medications & More During Pregnancy and Breast-feeding. MotherToBaby website. https://mothertobaby.org/. Accessed February 13, 2019; **Murphy VE:** Managing asthma in pregnancy. *Breathe (Sheff)*. 2015;11(4):258-67; **Tran TT et al:** Liver disease and pregnancy. *Am J Gastroenterol*. 2016;111:176-94.

AudioDigest

Internal Medicine
Board Review

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Preoperative Medical Evaluation

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Overview: *several reasons for preoperative consults*—identify risk factors; assess severity and stability of comorbid conditions; provide clinical risk profile for informed and shared decision making; make recommendations for management changes, for further testing, or specialty consultation; don't "clear" patients for surgery; should say patient in optimal medical condition for planned procedure

Diagnostic Studies and Laboratory Tests

Overview: indications generally similar to those if no surgery; do not order routinely; testing indicated when history and physical indicate needed for higher-risk procedures or when results will influence management; not indicated as screening or routine testing for minimally invasive or low-risk surgeries when recent studies done and unlikely to have changed, and when results will not influence perioperative management

Complete blood count (CBC): reasonable to get hemoglobin if signs or symptoms of anemia, history of anemia, or diseases usually associated with anemia (*eg*, malignancy or chronic kidney disease), and if having major surgery with expected significant blood loss or need for transfusion; white blood cell (WBC) count helpful if signs or symptoms of infection, history of myeloproliferative disorders, or recent chemotherapy; platelet count useful if suspected abnormal hemostasis, or if conditions or drugs that predispose to thrombocytopenia or thrombocytosis; prothrombin time (PT) (international normalized ratio [INR]), and partial thromboplastin time (PTT), should only be done if coagulopathy suspected or if patient taking anticoagulants (eg, warfarin, heparin); INR necessary to guide perioperative anticoagulation management

Exceptions: many obtain these tests for intracranial or spine surgery because believe little bleeding would be disaster; however, no good evidence that these tests predict bleeding

Chemistry: basic or comprehensive metabolic panel; electrolytes may be indicated if history suggests conditions likely to be associated with abnormalities (eg, sodium, potassium); some of these diseases include chronic kidney disease, heart failure (HF), adrenal insufficiency; also if patient on medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocking agents (ARBs), or diuretics, known to affect electrolytes; glucose reasonable if symptoms or risk factors for diabetes (*eg*, polydipsia) or if on steroids; useful in those with known diabetes to assess control and guide management

Renal function tests: blood urea nitrogen (BUN) and creatinine potentially useful in elderly, those with chronic kidney disease, possibly those with hypertension, diabetes, taking medications adversely affecting function, and sometimes those undergoing major surgery

Liver function tests: valuable only if acute hepatitis suspected

Urinalysis: evaluate and treat patients with genitourinary (GU) symptoms; may be beneficial to screen for and treat asymptomatic bacteriuria in those undergoing urologic surgery with instrumentation of GU tract; not indicated before joint replacement

Electrocardiogram: potentially useful in patients with known cardiac disease or suspicion of cardiac disease if undergoing major or intermediate- to high-risk procedures, or sometimes use American Society of Anesthesiologists (ASA) Class III or IV; not indicated solely based on age or as baseline for comparison; although many abnormalities found, rarely change management

Chest x-ray: almost never indicated; only if active or suspected cardiopulmonary disease based on history and abnormal chest exam

Perioperative Medication Management

Overview: consider pharmacokinetics, effect on primary disease, if there will be clinical deterioration or withdrawal symptoms, and effect of medication on perioperative risk including potential drug interactions with anesthetics; most medications can safely be continued; some considered essential (*eg*, cardiac medications, pulmonary medications, steroids) and should be continued; many need not be continued (optional); others require discontinuation or dose adjustment (*eg*, hypoglycemics, anticoagulants, antiplatelet drugs); others may need to be started prophylactically; some physicians give only what they deem necessary and others do as little as possible to disrupt usual regimen

Medications to continue: cardiopulmonary medications should generally be continued; includes antihypertensive, antianginal, and antiarrhythmic drugs; continue beta blockers, statins, and clonidine; continue inhalers (beta agonists, anticholinergics, and steroid inhalers)

Exceptions or controversial medications in this category: diuretics often withheld on morning of surgery from concern that patients might become hypovolemic or hypokalemic; does not happen with chronic diuretic therapy, but typically stop them anyway (diuretic effect lasts >24 hours anyway); also ACE inhibitors and ARBs, which have been associated with more hypotension particularly during induction of anesthesia, but not necessarily increase in "hard outcomes";

anesthesiologists in particular like to have these drugs withheld on morning of the surgery; if you stop them, restart postoperatively

Rheumatologic medications: including DMARDs and biologics; 2017 guidelines by American College of Rheumatology (ACR) and American Association of Hip and Knee Surgeons; controversial; consult patient's rheumatologist; consider half-life of drug and dosing schedule, as well as disease severity and control; for simpler medications, NSAIDs, typically stop 1 day to 3 days before surgery because of possible bleeding or renal effects; celecoxib (COX-2 inhibitor) does not affect platelets or cause bleeding; methotrexate and hydroxychloroquine typically continued perioperatively; TNF-alpha inhibitors problem; includes infliximab and adalimumab; tend to stop ~2 wks before surgery; resume ~2 wks after, assuming adequate wound healing; speak to rheumatologist, review history

Psychiatric medications: usually continue despite potential concerns; SSRIs have potential for bleeding (platelet dysfunction); tricyclics may be associated with arrhythmias, lithium with nephrogenic diabetes insipidus; MAO inhibitors exception, particularly older ones (have been associated with serotonin syndrome and hypertension); typically stopped 10 days to 14 days before surgery

Herbal medications: in theory, should be stopped 1 wk to 2 wks before surgery because may be associated with bleeding, sedation, hypoglycemia, drug interactions; include drugs like ginseng, garlic, ginkgo biloba, etc; in practice, many patients undergo surgery have taken these drugs recently because physician did not obtain complete medication history or patient did not want to reveal use of these medications

Cardiac Risk

Urgency: emergency operation means patient has to go to operating room (OR) in <6 hrs; urgent procedure, 6 hrs to 24 hrs (lecturer extends to 48 hrs); time-sensitive procedure can be delayed ≤6 wks; elective can be delayed ≤1 yr or not done

Risk: guidelines have changed from low-, intermediate-, and high-risk categories; now combined surgical and patient characteristics; define low risk as having <1% chance of major adverse cardiac events (MACE); elevated risk ≥1% change of MACE; (lecturer preference low, intermediate, and high risk; someone with risk of 1% to 2% may not be treated same as someone with 10% to 15% risk)

Risk calculators: 3 types of risk calculators used

Revised cardiac risk Index (RCRI): most commonly used; by Tom Lee and colleagues; derived from >4300 patients aged ≥50 yrs undergoing major cardiac surgery, with expected length of stay of ≥2 days; should not be used for minor surgery or ambulatory procedures because will overestimate risk; *6 independent predictors of major cardiac complications* — high-risk surgery, history of ischemic heart disease, HF, stroke or TIA, diabetes treated with insulin, and renal insufficiency (defined as creatinine >2); *predicted complications* — in-hospital complications, not 30 days; included myocardial infarction (MI), pulmonary edema, ventricular fibrillation, cardiac arrest, and complete heart block during hospitalization; patients grouped by number of risk factors; more risk factors meant higher risk; with new ACC guidelines, 0 or 1 risk factor, risk <1% (low risk); having ≥2, elevated risk; good at separating low- vs high-risk patients but underestimates risk in aortic aneurysm surgery

MI or Cardiac Arrest (MICA) Risk Calculator: MICA; published by Gupta and colleagues; used National Surgical Quality Improvement Project (NSQIP) database to develop and validate it, using each one with several hundred thousand patients; 5 predictors of complications MI and cardiac arrest; did not include pulmonary edema; 30-day endpoints, not in-hospital complications; *predictors* — type of surgery, dependent functional status, renal insufficiency (defined as creatinine >1.5, not >2 as in RCRI), ASA class, and increasing age; not true comparison to RCRI because different endpoints; believed it to be better discriminative and predictive ability for MI or cardiac arrest

American College of Surgeons (ACS) NSQIP Surgical Risk Calculator: published by Bilimoria and colleagues; most comprehensive and more cumbersome; need to know Current Procedural Terminology (CPT) code for procedure (of >1500 procedures); ~20 variables; predicts cardiac risk, mortality, serious complications, any complications, pulmonary complications, others

Using algorithm: define if patient at low or elevated risk; plug that into algorithm published in 2014 guidelines; Perioperative Cardiac Assessment for Coronary Artery Disease algorithm

First step: asks if need for surgery emergent; if yes, no time to do more than brief clinical risk stratification, maybe make medication recommendations, then proceed to surgery

Second step: asks if patient had recent acute coronary syndrome (ACS); if yes, highest-risk group; used to be called "major clinical predictors" in previous guidelines; if recent ACS, need to be evaluated and treated according to guideline or goal-directed medical therapy; should have some form of cardiac evaluation, either stress test or cardiac catheterization; should be on aspirin, beta blockers, statins, etc; should be stabilized before they go anywhere; used to include valvular heart disease, HF, and arrhythmias (now have their own guidelines and removed from this algorithm in latest ACC guidelines)

Third step: assuming no recent ACS, estimate risk of MACE using one of calculators noted earlier; if low risk (<1%), proceed to surgery; if elevated risk, determine functional capacity; determine if moderate or greater; determine whether can do equivalent of ≥4 metabolic equivalents of tasks (METs) (*eg*, climb flight of stairs or walk 2 to 4 blocks at good pace, without any symptoms); those who can do that tend to do well and should proceed to surgery; physician evaluation of exercise capacity or patient's self-reported exercise capacity has been questioned; new study, METs Trial, may change this

Next steps: assuming patient can't do 4 METs, or unknown what they can do, gray area; ask if further testing will impact decision making or perioperative care; if patient wants surgery regardless or needs surgery with no other option, may proceed to surgery or consider alternative strategies; goal not necessarily stress testing and coronary revascularization; other options to be considered include lesser surgical procedure, maybe nonsurgical option, or no surgery if elective; if you think further testing will change management, proceed

to pharmacologic stress testing; if normal, proceed to surgery; if abnormal, consider coronary revascularization

Canadian Cardiovascular Society guidelines: do not recommend stress testing at all; for emergency or urgent surgery, recommend postoperative troponins and electrocardiography; recommend considering in-hospital shared care management or comanagement; if elective, use RCRI; if RCRI score ≥1, if aged ≥65yrs, or if aged 45 yrs to 64 yrs with significant cardiovascular disease, recommend preoperative brain natriuretic peptide (BNP) or end-terminal proBNP; if results in normal range (<300 pg/mL for end terminal pro BNP and <92 pg/mL for BNP), no further testing or routine monitoring; if elevated or not available, recommend postoperative troponin, electrocardiograms, and shared care management

Types of stress testing: pharmacologic stress test if elevated risk; fewer false positives with dobutamine stress echocardiogram, but more physiologic; increases heart rate and blood pressure and gives ischemic threshold; or can get dipyridamole or adenosine nuclear imaging test; preferred for patients with left bundle branch block, but relatively contraindicated in those with chronic obstructive pulmonary disease (COPD) and bronchospasm because dipyridamole and adenosine may cause bronchospasm; fairly comparable; poor positive predictive value only 1 in 5 or 1 in 6 with positive test go on to have postoperative cardiac complication; most patients do well, even with positive test; negative predictive value >95%; negative test in person with high pretest probability may be false negative

Resting 2-D echocardiograms: play no role in predicting risk of ischemic heart disease in surgery; should be used only for evaluating patients with valvular disease or HF

Left ventricular (LV) function: ACC guidelines say reasonable for patients with dyspnea of unknown etiology, or for patients with HF who have worsening dyspnea or change in clinical status; routine preoperative evaluation of LV function not recommended, not shown to have benefit

Stress testing: guidelines say reasonable if elevated risk, poor functional capacity (<4 METs), if results will change management; routine screening with noninvasive stress testing not useful for low-risk noncardiac surgery; routine preoperative coronary angiography not recommended

Management: 2 options if elevated risk, prophylactic coronary intervention and medical therapy

Prophylactic coronary intervention: prophylactic coronary revascularization, coronary artery bypass grafting, (CABG), or percutaneous coronary intervention (PCI); no evidence of better outcome vs medical therapy alone with either of these regimens because risk of revascularization; 2 randomized controlled trials of prophylactic coronary intervention before noncardiac surgery; *CARP Trial (Coronary Artery Revascularization Prophylaxis)* — by McFalls and colleagues 2004; 510 patients with stable cardiac disease scheduled to undergo elective vascular surgery; randomized to medical therapy with or without revascularization; no difference in 30-day MI or death; no difference in primary outcome of long-term mortality ~2.5 yrs later; in revascularized subgroup, patients with bypass surgery seemed to do somewhat better than those with PCI, presumably because more complete revascularization; no difference between that and medical therapy; *DECREASE-V Trial pilot study* — Poldermans group (Netherlands) has been questioned; 101 patients with abnormal dobutamine stress echoes with ≥5 segments abnormal, previously shown not to benefit from beta blockers; randomized to medical therapy with or without revascularization; no difference in 30-day mortality or MI, and no difference in mortality at 1 yr; if patient had been previously revascularized, survived, asymptomatic, and currently medically stable, may be potentially beneficial compared with person who never had revascularization; from registry from Coronary Artery Surgery Study (CASS trial)

Guidelines: revascularization before noncardiac surgery recommended in cases where revascularization would otherwise be indicated according to existing clinical practice guidelines; not recommended exclusively to reduce perioperative cardiac events; *ACC guidelines updated in 2016* — Levine and colleagues; concern about stent thrombosis after PCI; recommend that elective noncardiac surgery should be delayed ≥30 days after bare-metal stenting, and optimally 6 mos after drug-eluting stent implantation; elective noncardiac surgery after drug-eluting stent placement in patients in whom P2Y12 inhibitor must be stopped may be considered after 3 mos, but if risk of further delay of surgery greater than expected risk of stent thrombosis; European Society of Cardiology goes down as low as 1 mo (most do not do that); if stent had been placed in setting of acute coronary syndrome, recommendation for dual antiplatelet therapy for 12 mos and that has not factored in guidelines; need to consider because higher risk of stent thrombosis in those patients; guidelines say may be reasonable to continue aspirin when potential for increased cardiac events outweighs risk of bleeding; initiation of aspirin not beneficial

Antiplatelet therapy summary: lecturer typically continues aspirin for patients using it for secondary prophylaxis, even though POISE-2 study said not to do so; for patients with recent stents, continue dual antiplatelet therapy for recommended duration; in patients with previous PCI who have completed course of dual antiplatelet therapy, continue aspirin perioperatively; subgroup analysis on POISE-2 found that patients in this subgroup benefit from continuing aspirin, with 50% reduction in MIs compared with those who stopped

Stopping antiplatelet therapy: if surgery mandates discontinuation, typically stop aspirin 3 days to 7 days before surgery, clopidogrel 5 days to 7 days before, prasugrel 7 days before, ticagrelor 5 days before; ticagrelor reversible platelet inhibitor

Beta blockers: perioperative beta blockers controversial; mixed results of meta-analyses; found to be beneficial in reducing ischemia and MI; harmful in increasing risk of stroke as well as hypotension and bradycardia; mixed results for total mortality; guidelines recommend continuation in patients using them chronically; if ischemia on stress test or if ≥3 or more RCRI risk factors, may be reasonable to begin perioperative beta blockers; if starting beta blockers before surgery, do so ≥1 day before; recommend ≥1 wk to 2 wks before; do not start on day of surgery (shown to be harmful in POISE study); more cardioselective drugs may be better than metoprolol; beta blockers found to be beneficial

in several large observational studies (as opposed to randomized control trials, which were mixed); prophylactic beta blockers rarely started now

Statins: continue in patients currently on them who are undergoing noncardiac surgery; reasonable to initiate in patients undergoing vascular surgery; perioperative initiation may be considered in patients who have clinical guidelines according to goal- or guideline-directed medical therapy undergoing elevated-risk procedures; consider starting in patients with diabetes, peripheral arterial disease, hyperlipidemia going for elevated-risk procedures; probably use more potent statin; perhaps ≥50% of maximum dose initially; may be benefit in starting early, even 24 hrs or 1 wk before; no evidence of harmful effects

Alpha-2 agonists (*eg*, clonidine): not recommended for prevention of cardiac events; no benefit; no reduction in perioperative MI and death; increased nonfatal cardiac arrest and perioperative hypotension; do not start prophylactically; if patient using, continue to avoid rebound

ACE inhibitors: ACC guidelines say continuation of ACE inhibitors or ARBs reasonable; if withheld before surgery, restart as soon as possible postoperatively; associated with hypotension with induction of anesthesia; typically continued for patients with HF or uncontrolled hypertension; otherwise, usually withheld on morning of surgery

Pulmonary Risk

Overview: postoperative pulmonary complications more common than cardiac complications; risk factors divided into patient-related and procedure-related; ACCP guidelines considered outdated (published 10 yrs ago)

Patient-related risk factors: in general health status category, age, functional dependence, and ASA classification risk factors; impaired sensorium can increase risk, as well as HF; COPD, cigarette smoking, obstructive sleep apnea, and pulmonary hypertension potential risk factors; screen all patients for sleep apnea using STOP-Bang score; if ≥5, plus if elevated bicarbonate, highest-risk sleep apnea patients; may be treated differently from those with lower score or not known to have sleep apnea; most risk factors not modifiable

Procedure-related risk factors: surgical site one of most important; proximity to diaphragm; intrathoracic surgery, in particular with lung resection, and upper-abdominal surgery, highest-risk procedures for postoperative pulmonary complications; type of operation and surgical technique may play role; type of anesthesia another potential risk factor; some controversy, but felt more risk for general than neuraxial anesthesia; other risk factors include duration of surgery and anesthesia, emergency surgery (always increases risk), and postoperative factors including analgesics and narcotics, presence of nasogastric (NG) tube, and use of long-acting neuromuscular blockers

Laboratory testing: spirometry rarely indicated; main use would be for patient with dyspnea or hypoxia of unknown etiology; preoperative pulmonary function test before lung resection to estimate what residual they will have (but rarely changes management); maybe in patient actively wheezing (when unknown if wheezing and if they have good or poor FEV_1); chest x-ray rarely helpful, should not be obtained; serum albumin may be predictor; pulmonary risk indices published but not widely used; some ways to predict postoperative pulmonary complications (*eg*, Canet score); Arozullah and Gupta have published risk indices for postoperative pneumonia and respiratory failure; ACS NSQIP calculator also predicts pulmonary complications

Surgery-related risk factor summary: thoracic and upper-abdominal procedures, aortic aneurysm, neurosurgery, emergency surgery, general anesthesia, prolonged surgery, and albumin <3.5 g/dL

Reducing risk: mainstay, postoperative lung-expansion modalities (*eg*, deep breathing exercises and incentive spirometry); do not routinely use NG tubes (try to remove as soon as possible after surgery); use short- rather than long-acting neuromuscular blockers if needed; try to get patients to stop smoking 1 mo to 2 mos before surgery

Venous Thromboembolism (VTE), Deep Vein Thrombosis (DVT), and Pulmonary Embolism (PE)

Screening: many surgical patients at risk; should all be screened; use Caprini or Rogers score; main risk factors for VTE include older age, orthopedic surgery or trauma, past or current history of cancer, prior VTE, thrombophilia, and immobilization; other risk factors as well; scoring systems all assign different points

American College of Chest Physicians (ACCP) guidelines: published in 2012; *4 categories of patients* — very low risk (0.5%); low risk (1.5%); moderate risk (3%); high risk (6%); based on Rogers and Caprini scoring systems; for very low risk, recommend early ambulation; for low risk, recommend mechanical prophylaxis with intermittent pneumatic compression or sequential compression devices; for moderate and high risk, pharmacologic therapy; for moderate risk, low-dose unfractionated heparin or low-molecular-weight (LMW) heparin; for high bleeding risk, mechanical prophylaxis; for highest-risk group, LMW weight heparin or low-dose unfractionated heparin plus mechanical prophylaxis; for total hip or knee replacement, recommended agents include LMW heparin, any direct-acting oral anticoagulants (DOACs; *eg*, apixaban, dabigatran, rivaroxaban), fondaparinux, low-dose unfractionated heparin, adjusted-dose coumadin, aspirin; combine with pneumatic compression devices; for knees, recommend duration 10 days to 14 days; for hips, recommend extended-duration prophylaxis ≤35 days; for patients undergoing abdominal surgery for cancer (gynecologic and gastrointestinal [GI] cancer surgery), recommend 28 days of prophylaxis

Patients on full-dose anticoagulation: balance risk of bleeding with continued drug vs risk of thromboembolism if stopped; risk of bleeding affected by anticoagulation regimen, type of surgery, and patient comorbidities or risk factors; need to know reason patient on anticoagulation; *ACCP table for risk stratification for perioperative thromboembolism* — defines patients as low, moderate, or high risk for based on indication for anticoagulation; includes mechanical heart valve, atrial fibrillation (Afib), or VTE; for high-risk patients, suggest considering bridging therapy; for mechanical heart valves (includes mitral valve prosthesis or older aortic valves) as well

as patient with recent stroke; *Afib category* — said Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke (CHADS2) scores of 5 or 6, but before BRIDGE study questioned whether these patients benefit from anticoagulation; 2017 ACC guideline recommended it for patients with CHADS vascular disease (VASc) scores ≥7, or stroke; for VTE category, if DVT or PE within 3 mos, or severe thrombophilia, recommended bridging; no studies showing decreased thromboembolism using bridging therapy, but increased bleeding risk

Warfarin: *options* — continue, discontinue, or subcutaneous heparin prophylaxis, then resume warfarin postoperatively; for bridging therapy, stop warfarin ~5 days before, give either LMW heparin, (more commonly used), or intravenous unfractionated heparin perioperatively while INR subtherapeutic; LMW heparin stopped 24 hrs before surgery; resume warfarin as soon as possible after surgery

DOACs: can be either continued or stopped; no need for bridging; short half-lives; stop 1 day to 3 days before

Procedures that can be performed without stopping anticoagulation: dental procedures, GI procedures (upper endoscopy and colonoscopy without biopsy or without polypectomy; some gastroenterologists do biopsies and polypectomies on full anticoagulation); ophthalmologic surgery typically does not require stopping anticoagulation

Stopping DOAC: consider bleeding risk of procedure and renal function (either >50 cm3/min for creatinine clearance, or below, usually 30-50 cm3/min); if normal renal function and low risk, usually stop drugs ≥1 day before (*ie*, do not take on morning of surgery or day before); last dose 36 hrs before; for high-bleeding-risk procedure or impaired renal function, 2 days before; both impaired renal function and high bleeding risk, 3 days before

Urgent surgery: reversal agents for DOACs include idarucizumab (for dabigatran) and andexanet alfa (for rivaroxaban and apixaban)

Restarting DOACs or bridging postoperatively: if low-bleeding-risk procedure, can restart anticoagulation 24 hrs postoperatively; if high-bleeding-risk procedure, wait ≥48 hrs to 72 hrs, or when adequate hemostasis, and when okay with surgeon; in interim, can use pharmacologic VTE prophylaxis; should not use bridging therapy with DOACs (they achieve full anticoagulation in 1 hr to 4 hrs)

Other Hematology

Anemia: associated with increased perioperative morbidity and mortality; ideally, evaluate and treat preoperatively; if hemoglobin <10 g/dL, and expected blood loss from surgery will lower it to <8 g/dL, and want to avoid transfusion, may intervene preoperatively; other reason to delay and address, suspected malignancy or major hematologic disorder

Perioperative management: depends on etiology; can correct nutritional deficiencies; can give iron if deficient or on erythrocyte stimulating agents; can give red cell transfusion; American Association of Blood Banks recommends transfusion if hemoglobin is <7 g/dL, if hemodynamically stable and asymptomatic, or transfuse with hemoglobin <8 if underlying cardiovascular disease, or after cardiac or orthopedic surgery

Thrombocytopenia: indications for surgical delay include new significant thrombocytopenia with platelet count <50,000, or recent 50% decrease with platelet count <150,000, or if possibly related to microangiopathic hemolytic anemia, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, etc; if <20,000, can have excess bleeding with low-risk surgery; if <50,000, excess bleeding with most surgeries; <100,000 (80,000-100,000 minimum) for cardiac or neurosurgery; for perioperative management, transfuse as necessary to achieve levels; 1 unit of platelets increases platelet count 20,000 to 30,000; lifespan ~3 days

Endocrine Disorders

Diabetes: target glucose perioperatively 140 mg/dL to 180 mg/dL; tight control associated with hypoglycemia and bad outcomes; recommended regimen for insulin, basal bolus plus correction dose; withhold oral hypoglycemics on morning of surgery; in patient on basal insulin, usually continue full dose but may decrease if history of hypoglycemia, decreased caloric intake, or chronic kidney disease; more current recommendation almost suggesting slight decrease of 10% to 20% preoperatively (other guidelines say not to change); if patient on neutral protamine Hagedorn (NPH) insulin, typically give one-half to two-thirds and hold all short-acting insulin on morning of surgery

Thyroid disease: mild to moderate hypothyroidism okay, no increased risk; hyperthyroidism has risk of thyroid storm if not treated; continue medical therapy for hypothyroidism, so continue levothyroxine; for hyperthyroidism, continue beta blockers, propylthiouracil, or methimazole; ideally, have patient euthyroid preoperatively

Adrenal disorders and patients on steroids: continue corticosteroids and mineralocorticoids; consider supplemental or stress-dose steroids; hypothalamic-pituitary-adrenal (HPA) axis not inhibited on any dose <3 wks, alternate-day therapy, or <5 mg prednisone or equivalent; impaired with ≥20 mg prednisone, Cushingoid appearance, or primary adrenal insufficiency; unclear for intermediate range (5-20 mg prednisone); options include cosyntropin, or ACTH stimulation test, baseline cortisol, or give empiric steroids without testing; dosing based on stress of procedure; no evidence for or against stress-dose steroids; if low-stress procedure, can continue usual steroids or give 25 mg hydrocortisone preoperatively; if intermediate-stress procedure, 50 mg hydrocortisone then 25 mg every 8 hrs for 1 day; if high-stress procedure, 75 mg to 100 mg hydrocortisone then 50 mg every 8 hrs for 1 day to 3 days

Liver Disease

Overview: risk of perioperative complications; magnitude depends on type, severity, procedure (most important, and type of anesthesia; evaluate with Child-Pugh classification or model for end-stage liver disease (MELD) score

Child-Pugh classification: *5 parameters* — ascites, bilirubin, albumin, PT or INR, and encephalopathy on 1- to 3-point basis; 5 to 6 points class A, okay; 7 to 9 class B; 10 to 15 class C, avoid elective surgery

MELD score: includes bilirubin, INR, and serum creatinine; score <8 okay; 8 to 14 intermediate risk; ≥15 means elective surgery contraindicated

Management: patients with mild to moderate chronic liver disease without cirrhosis (includes patients with mild chronic hepatitis or fatty liver) tolerate surgery well; optimize medical therapy; highest-risk patients should postpone elective surgery; includes acute hepatitis, either alcoholic, viral, or drug induced (includes Child-Pugh class C, MELD score ≥15, fulminant hepatic failure, and severe coagulopathy); try to correct PT to within 3 secs of normal with vitamin K or fresh frozen plasma; maintain platelet count ≥50,000 to 100,000; treat ascites with diuretics or drainage; correct electrolytes; provide nutritional support

Renal Disease

Overview: shared risk factors with cardiac disease; risk for cardiac complications; control risk factors; avoid nephrotoxic drugs; adjust doses of renally metabolized drugs; dialyze patient day before (not morning of) surgery; consider checking potassium on morning of surgery

Neurologic Disease

Overview: continue most neurologic medications (*eg*, antiepileptic drugs for seizures and parkinsonian medications); postoperative stroke risk generally low for most noncardiac, nonneurologic surgery

Risk factors: type of procedure most important; highest risk valve replacement, bypass surgery, or combined procedure; carotid endarterectomy high risk; vascular surgery in general higher risk; prior stroke risk factor for postoperative stroke; also Afib, age, and hypertension; try to delay surgery ≥3 mos after stroke

Suggested Reading

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Pain Management

Timothy Deer, MD, *Professor of Anesthesiology, West Virginia University School of Medicine, Morgantown, West Virginia*

Overview: pain is a major problem in the US; many know about this because of the opioid crisis and also because of difficulty with function and the cost to society; estimated that 100 million people in the US suffer from chronic pain, including, eg, low back pain, neck pain, and migraine headaches; these syndromes cause both social and economic problems; has led to a focus on chronic pain in order relieve suffering, reduce the risk of addiction, lower the cost of care, and improve the quality of care

Types of pain: acute pain means there is a pain-causing injury or tissue abnormality that began in the recent past; acute pain has been defined as a pain that is consistent with the tissue trauma or tissue disease state at hand; most people would say that acute pain should resolve within 3 months; if acute pain lasts longer than 3 months, many would characterize this as chronic pain, though prefer 6 months as an endpoint; need to reduce the use of opioids has made the 3-month definition more popular; another definition of acute pain versus chronic pain is that acute pain is consistent with the tissue trauma or injury, whereas chronic pain is pain that persists after a normal tissue injury would have resolved either with minimal treatment or on its own

Nociceptive pain versus neuropathic pain: nociceptive pain is usually dull or aching, often consistent with conditions like arthritis, where the pain is focal and tends to occur with movement or mechanical position, such as standing; neuropathic pain is often characterized as burning, stinging, or shooting, and is characteristic of nerve pathology, such as carpal tunnel syndrome or peripheral neuropathy; in carpal tunnel, the hand hurts in the median nerve distribution; in peripheral neuropathy, the nerves of feet or hands function abnormally because of diabetes or other causes

Mixed pain syndromes: this 3rd class of pain is probably more common than we suspect; it is a mixture of nociceptive pain, where the nociceptors cause a dull, achy pain, and neuropathic pain, which is burning or lancinating; mixed pain syndrome is difficult to treat in some cases and can be the reason some people fail different treatment options; thus, it is important to have multimodal pain therapies; such therapies may include, for example, physical therapy combined with nonsteroidals combined with anti-neuroleptics combined with interventional procedures such as injections

Pain Treatment

Overview: definition of pain as defined by the International Association for the Study of Pain in 1964 is an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage

Emotional response: every component of pain has some emotional component; for example, some people do not have a negative response to pain experienced during endurance sports; in contrast, if someone who does not cope well with pain stubs a toe, they may be disabled for weeks from this simple injury; this emotional and societal component of pain needs to be taken into account in the algorithm of pain treatment, and we need to treat people differently based on their societal needs and the people they are surrounded by; for example, someone with back strain at work may do well with physical therapy, over the counter medications, and rest; don't recommended more than 2 days of rest, though, for any back injury, because people can get atrophy and stiffness of their muscles; algorithm should always start simple, with physical medicine approaches, such as chiropractic care, over-the-counter medications, and, if needed, non-opioid oral medications; will focus today on what to do when those over-the-counter medications, physical therapy, transcutaneous electrical nerve stimulation (TENS) units, biofeedback, and other simple treatments are not helpful; important time in US to focus on interventional therapies associated with and used as multimodal therapy, including physical medicine; includes different types of interventions for different disease states

Psychological treatments: important to treat the emotional component of pain; may include counseling; in biofeedback psychologists teach people to use their own mind to help them control their response to pain; in psychotherapy, you analyze your life to see how that may complicate your pain; may use psychiatric medication for things like depression; anytime depression is associated with pain or anxiety, it would be helpful to consult with someone in those fields; in many cases, such as acute disc herniation, however, those components are not a major part of the pain presentation or the pain treatment

Interventional therapies for chronic pain: multimodal therapies require a multimodal team; includes physician, nurse practitioner, physician assistant, nursing staff, and in many cases, social workers who may help with insurance, or other consultants, such as neurosurgeons, anesthesiologists, or physiatrists; may also consult with infectious disease specialists, for example, if there has been an infection of the spine or nervous system; the most common physicians performing interventional pain therapy are board certified anesthesiologists who have done a

fellowship in chronic pain medicine; these fellowships are certified by the American College of Graduate Studies and usually require 1 yr of training under the tutelage of someone in that type of program and involve exposure to anesthesiology-based, psychiatry-based, neurology-based, rehabilitation-based, and surgery-based pain approaches; these types of physicians are prominent throughout the country; many nursing personnel will find themselves working with this type of clinician as they implement this multimodal therapy philosophy

Spine: the most common procedures in America done for chronic pain are in the spine; spondylosis is a disease of the joint that causes pain in the axial skeleton, the cervical, thoracic, or most commonly, the lumbar spine; pain is worsened by extension or rotation of the spine, when the patient stands up straight or turns the body, and is often improved by leaning forward or sitting down; in contrast, spinal stenosis causes buttock or leg pain on standing

Joint disease: the most common treatments are physical therapy and interarticular joint injections, in which an x-ray is taken and the doctor puts a needle in the joint using x-ray guided fluoroscopy; if this is successful, it may be the only treatment needed, particularly in acute nerve or joint injury

Radiofrequency ablation: in more chronic disease, for example with severe arthritis, radiofrequency ablation can be effective; this is an established, FDA-approved, Medicare-approved therapy for treating chronic joint pain of the cervical, thoracic, and lumbar spine; the procedure requires a diagnostic block with local anesthetic of the medial nerve that innervates the joint from above and at the same level as the joint; if this provides relief that lasts from 1 to 6 hr, and this result is achieved on a second occasion, there is about an 85% chance that radiofrequency ablation of the nerve will cause a long-term response lasting from 6 to 24 months; the procedure is performed by placing the probe parallel to the route of the nerve under fluoroscopic guidance with anterior-posterior (AP), oblique, and lateral views, testing with a computer to make sure that the nerve being captured is a sensory, not a motor nerve, and burning for 90 sec to make the nerve nonfunctional for a period of time; has to be repeated in 12 months on average; this is in contrast to nerve ablation in the heart, which can terminate an arrhythmia for considerably longer; difference is that the tissues surrounding the ablation area in the heart are cardiac, not nerve, tissue; in the spine, there are nearby motor nerves and other sensitive structures, so can't use the intensity needed to destroy the nerve permanently; called a facet rhizotomy; common method of treatment; can be very helpful in people like diabetics who can have long-term glucose-control problems with steroids; thus,radiofrequency ablation usually reserved for chronic joint paint that doesn't resolve with injection or for patients who are high risk with intravenous (IV) or oral steroids

Spinal stenosis: occurs most commonly in the lumbar spine but can also occur in the cervical or thoracic spine; lumbar spinal stenosis is most common; spinal canal is encroached upon by a structure; can be bony stenosis from the frame and the pedicle of the vertebral body; can be discogenic stenosis from the disc protruding backward; can be ligamental stenosis from ligamentum flavum hypertrophy compressing the nerve, most commonly when the patient stands or walks; can be classified as mild, moderate, or severe stenosis based on the degree of disease in the patient's spine on MRI or CT scanning

Neurogenic claudication: spinal stenosis that progressively worsens with walking or standing; often improved by leaning on a shopping cart (the shopping cart sign) or sitting down

Open laminectomy: most common treatment in the US has been open laminectomy with or without fusion; this is a fairly major surgery performed in an often elderly population; still the most indicated treatment for severe stenosis

Other treatments for spinal stenosis: in recent years, 2 minimally invasive treatments have received FDA approval; these are often done by an interventional pain specialist such as an anesthesiologist

Spacer: this method involves placing a spacer between 2 spinous processes to open the canal, keeping the spine from extending past a certain point; this is popular for patients who have mild-to-moderate stenosis, that have neurogenic claudication that is progressive, who have failed physical therapy, medications, and often injections, and who have a space between the spinous processes that will allow a spacer to be placed by means of a minimally invasive tube-like structure; done in patients who would like to avoid more major surgery because their disease is not severe enough to warrant the risk, or whose medical condition makes them ineligible for major surgery; currently, 5-yr data on interspinous spacers shows efficacy around 80% at 5 yrs; a surgical open technique called X-STOP that was compared with the spacer did not show the same results either from an efficacy standpoint or a complication standpoint; part of going forward with the spacer is to obtain a flexion-extension film to make sure there is no more than grade 1 spondylolisthesis

Spondylolisthesis: joint condition where the joints are no longer holding together and the spine is moving; comes in grades 1 through 4; grades 3 and 4 almost always require open surgical fusion; grades 1 and 2 can often be treated conservatively with facet ablation or other procedures, but above grade 1, spacers may be contraindicated

Minimally invasive lumbar decompression ("MILD") procedure: recently approved by the Center for Medicare Services and the FDA; involves placing a small epidural needle in the spine, performing an epidurogram to see the area of stenosis, and then entering the ligament with a device that takes ligament out in small pieces to decompress the stenosis; indicated when a patient has a more than 2.5 mm thickening of the ligament compressing the spine with standing or walking; has shown promise in the US and has been used in parts of Europe to try to reduce the need for open decompression, in which the ligament is totally removed and hardware is placed; MILD has been successful in many patients, who have been enabled to perform their normal functions, stand, and walk longer distances; efficacy has been shown in a multicenter prospective study in the US

Summary: both the spacer technique and the ligament decompression procedure have great promise but

are only appropriate in the right patient; in severe, multilevel stenosis, open surgical correction still may be indicated

Transforaminal injections: another interventional procedure performed in spinal stenosis is transforaminal injection around the foramen, an interspinous injection to the epidural space; this is similar to the anesthesia techniques used for childbirth or knee replacement surgery, but steroids are used instead of local anesthetic; another procedure is caudal injection, where a needle is placed in the sacral hiatus, the opening at the end of the sacrum; these procedures have provided some temporary improvement in patients and may be used as part of a rehabilitation tool to improve patients' status while they are undergoing physical therapy to improve strength; stenosis can cause weakening of the legs and the propensity to fall when walking long distances

Discogenic pain: nerve pain from the disc; radicular pain means the nerve is being compressed or irritated in the spine, causing pain in a limb; will focus both on cervical and lumbar radiculopathy, or radiculitis, in which the nerve is inflamed but not damaged; can be talked about in either part of the spine; when a disc herniates or protrudes and impinges on the nerve as it exits the spine, patients tend to get pain in the dermatome of that nerve; when they have dermatomal pain, there's often associated numbness, weakness, or loss of reflex

Treatment: normally involves placing steroid around the nerve to reduce inflammation and then getting the patient into a physical medicine program to change their body mechanics to help keep he problem from coming back; injections can also be used as a predictor for surgery to determine the level of the nerve compression; particularly valuable in patients who have multilevel disease, when the surgeon isn't quite sure which level to operate on; called a diagnostic block; in the lumbar spine, dexamethasone (Decadron) is often used because it is water soluble and presents the least risk to the spine; also used cervically and thoracically in most cases; no drug has been labeled by the FDA for epidural injection because these procedures have been done for over 40 years and no company has come forward to have their drug labelled; However, it is the standard of care used by physicians around the US, Europe, and Australia

Epidural steroids: best done under fluoroscopic guidance to assure the right location; techniques include interlaminal (between the lamina, in the middle of the spine), transforaminal (in the foramen where the nerve exits the spine), and caudal (in the sacral hiatus below the sacrum); all have been used for discogenic pain; no comparative study shows efficacy being better in one than the other; data suggest that transforaminal approaches have better efficacy in the lumbar spine than interlaminar approaches and that a transforaminal approach in the cervical spine has a higher risk than an interlaminar approach; some patients have no ligamentum flavum above C6-7; the ligament may be very thin or nonexistent; recommend interlaminar injections be done no higher than C6-7 or 7-1 in most cases and be done with a catheter if needed higher than C5-6; implicated as a cause of complications when people have gone in higher levels in the cervical spine, or via the anterior approach to the foramen

Muscle pain: one of the most common causes of pain; often associated with acute injury and can be treated with ice, physical therapy, and rest; chronic pain can occur in someone who walks abnormally and develops pain in the muscle, or who has pain in the neck that causes tension; most common treatments of chronic muscle pain are physical therapy, dry needling (although it has no scientific proof of efficacy), and massage therapy; often these cannot resolve the situation; in those cases, trigger points are often applied by many types of physicians, including family physicians, to reduce spasm in the muscle; only helpful if the patient follows up with a stretching program or massage program once the muscles relax; in severe cases where people have dystonia and trouble with abnormal movements, particularly in the neck or shoulder, different types of botulism toxin (Botox), of which there are 2 isomers, can be used; botulism toxin is also used in severe cases of torticollis, in which the patient can't move his/her head from severe spasm in the sternocleidomastoid muscle; another use of botulism toxin in these myofascial pain syndromes is for people who have cervicogenic headaches from the compression of the occipital nerve by the cervical spine muscles

Autoimmune work-up: consider autoimmune work up for chronic muscle pain; diagnosis of fibromyalgia, which is a nonspecific muscle pain, can be made; other diseases can exist, such as lupus, rheumatoid arthritis, or other autoimmune connective tissue disorders; in chronic multi-area muscle pain, reasonable to consider a referral to rheumatology or a rheumatological serology workup

Sacroiliac joint: connects the spine to the pelvis; weight bearing; often causes pain in the buttock, down into the leg, or into the groin; often misdiagnosed as a herniated disc or sciatica when the problem is in the joint

Diagnosis: joint will often show arthritis on the x-ray or MRI; if a person walks abnormally or limps because of an antalgic gait from a lower extremity problem, the SI joint will become inflamed and painful; muscle above the joint will become sore and reactive; often even difficult to examine because of tenderness; there are some exam techniques used, but the diagnostic gold standard is to put local anesthetic in the joint after an arthrogram under x-ray guidance; in an arthrogram, contrast is put into the joint and you either see the pattern of the joint spread, or see that the joint itself is not holding contrast because of severe degeneration

Treatments: options for SI joint pain include physical medicine (there are several protocols for physical therapy) and injection of the joint under x-ray guidance; radiofrequency ablation, where the joint is heated, can also be used; remember that the lateral branch nerves of the sacral nerve roots innervate the joint, so this is actually heated with a needle that goes to each area of the joint or one large probe that covers the entire area just above the periosteum, which is the lining of the bone near the joint; FDA has approved SI joint fusion as an option for chronic joint pain; done by a lateral approach where 3 screws are placed through the joint so it no longer moves; has been shown in initial studies to have good efficacy; new methods of fusing the joint involve putting a needle in the top of the joint and the

bottom of the joint, then placing a tube over the needle to place a type of device that will lock the joint in place so it doesn't move; less invasive, but studies are pending on the long-term efficacy; not uncommon to have both sacroiliac joint pain associated with radicular pain and other types of disease states, such as discogenic pain; all of these things can be present in the patient at one time; can have neuropathic pain from nerves and nociceptive pain from joint; recall previous discussion of mixed pain syndromes

- New therapies: these include platelet-rich plasma (PRP) and stem cells; regenerative medicine involves stem cells placed in the disc, in the joint, or around tissues; or patient's plasma is spun down until platelets become more predominant and then is reinjected into the patient; thought that there are growth factors in this protein-rich plasma that can cause healing around the joint and reduce inflammation; some studies have been done in single centers or a few centers that have been open label; the number of multicenter studies is quite limited for these therapies and include a few studies on intradiscal stem cells; early results are promising, but we cannot say at this point that intradiscal stem cells are indicated for disc disease, nor can we say that PRP is indicated for back pain; some evidence that PRP may improve tendonitis and make it heal more quickly, particularly when injected over 3 sessions over time; work being done to set standards for these types of therapies; need prospective, randomized studies to define who is the best candidate for regenerative medicine; lecturer thinks these procedures will become more common in the US over the next 5-10 years

Neuromodulation: as discussed, the traditional pain-control algorithm has been to start with over-the-counter treatments, then proceed to physical therapy, rest, non-opioid medications, and injections or procedures associated with physical therapy; in the past, next option was often opioids, which were then increased to high-dose opioids, with many people getting above 90 mg of morphine per day; this is above the CDC recommendation; we now have a crisis with opioids, which has caused death and disability, as well as substance abuse, cost to society, and increasing crime rates among those who are addicted; many people feel we need new solutions, and neuromodulation has become that solution in many areas; studies have shown that there is an opioid-sparing effect with neuromodulation, as well as that people on high-dose opioids do not do as well with that therapy

- Definition: neuromodulation is the use of either electricity or drugs to modify the neural responses of the spinal cord, peripheral nerves, or brain
- Deep brain stimulation: done as a part of neuromodulation for Parkinson's Disease for tremor; FDA-approved and commonly done; research being done currently on post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), depression, and obesity; vagal nerve stimulation has been used for epilepsy and depression; has been FDA approved and is used in certain centers as a common treatment; current work on non-invasive forms of stimulation of the brain and the vagal nerve shows promise
- Spinal cord stimulation: most common method of neuromodulation in the US; we place electrodes, much like pacemaker wires, in the spine, and then send a signal via computer, which is implanted under the skin, to stimulate the abnormal nerve function for pain; most common indications are for nerve damage from scarring after back surgery; also used for trauma to the nerve leading to conditions such as complex regional pain syndrome, which is a complicated condition where the nerve is no longer functioning normally and the limb gets hypersensitive, swells, has tissue changes, skin and hair changes, and atrophy; often used for other forms of nerve damage, such as peripheral neuropathy
- Types of spinal cord stimulation: spinal stimulation, dorsal root ganglion stimulation, and nerve stimulation; spinal cord stimulation is most commonly used therapy; has different waveforms, different frequencies, different computer software programs; used to treat patients for whom the other option might be high-dose opioids; efficacy studies have been done; level 1 evidence that spinal cord stimulation is successful for treating nerve pain of both the lower extremity, the axial back, cervical spine, and upper limbs for those who have burning pain of chronic nerve injury or neuropathy; for nociceptive pain, there is some evidence that it can treat things such as visceral pain from the abdomen or pelvis or other areas that may be not classic for stimulation; there has been success with these therapies in treating angina and heart failure by putting leads in the upper thoracic or lower cervical spine; becoming more and more common; studies have shown that this is cost-effective therapy compared to opioids and other medications; spinal cord stimulation has been shown to be superior to re-operation in chronic pain in those who have had failed back surgery
- Dorsal root ganglion stimulation: a small computer electrode is placed on a nerve from the spine that goes to an area that's been damaged; most efficacious therapy ever done in the field, as shown in ACCURATE study, led by Dr. Deer and published in the journal *Pain* in 2017; device is FDA-approved and commonly used not only for its original indication, nerve damage from trauma or surgery below the waist, but by physicians throughout the US, Australia, and Europe for things such as postherpetic neuralgia, post-thoracotomy syndrome, post-mastectomy syndrome, and other conditions where there is a focal nerve abnormality
- Peripheral nerve stimulation: placed on a computer chip or lead around a nerve in the periphery that's been damaged, such as the ilioinguinal nerve after groin surgery or the median nerve after carpal tunnel scarring; thought to be a low risk procedure; doesn't have the same efficacy data as that in the spine or dorsal root ganglion; level 1 studies ongoing trying to show improved efficacy of those devices; complication severity is quite small; use in many cases of very ill people has been promising; best study was done in those with post-stroke shoulder pain; device was placed around that area to help with both the pain and also the motor function around the axillary nerve
- Intrathecal drug delivery: another form of neuromodulation; we use chemicals in the spinal fluid to change the function of the spinal cord or nerve; the most common chemicals used that have been labeled by the FDA are morphine and ziconotide; ziconotide works on the calcium channels in the spinal cord; originally found

in a venomous snail of the Pacific Ocean; provided a great response for nerve pain and nociceptive pain; FDA-approved after 2004, when the study was presented in *JAMA,* showing efficacy and safety in patients over the course of a year; study was promising, but showed that at high doses sometimes people became unstable mentally, had terrible hallucinations, both auditory and visual, or had abnormal thoughts; when the FDA approved the drug, it was for chronic severe to moderate pain of both cancer and non-cancer origin; contraindicated in patients in whom there is a previous history of psychosis, schizophrenia, or unstable depression; doesn't affect respiratory centers; no cases reported of death from this drug or overdose causing respiratory collapse; in many centers, is first line therapy for those who have widespread or severe unrelenting neuropathic pain that doesn't respond to stimulation

Morphine: commonly used in an intrathecal pump because it can be used in much lower doses than the oral equivalent; with high-dose oral opioids, patient may be nauseous or drowsy; much lower rate of side effects when the equivalent doses are given intrathecally; studies, including the Landmark study in 2002, have shown that intrathecal drug delivery is superior to oral opioids for fatigue, diet, appetite, and overall feeling of well-being; several Polyanalgesic Consensus Conference papers, which have been published in *Neuromodulation* since early 2000s and updated about every 3 yrs, most recently in 2017, show that other drugs such as such as fentanyl, hydromorphone, and combinations using bupivacaine or clonidine are often better than morphine; the same is true for spinal cord stimulation and dorsal root ganglion stimulation; best practice consensus papers are in the *Journal of Neuromodulation*

Opioid Crisis

Overview: one reason for this lecture was to discuss multimodal therapies, algorithms, and interventional therapies that we should use to reduce the risk of opioids; there are some patients in the algorithm for whom opioids are appropriate; Centers for Disease Control has issued guidelines for opioids that suggest good safeguards

Benzodiazepines: limit using benzodiazepines and opioids together because of risk of respiratory depression; FDA overdose data show there is unquestionably an association between those 2 drugs; except for extreme or rare cases, recommend one or other be given and never use concomitantly

Morphine equivalent calculator: the FDA has found that over 50 morphine equivalents per day increases risk of overdose and death; risk even higher over 90 morphine equivalents per day; use a morphine equivalent calculator; for example, you can see how many hydrocodone tablets would equal 50 morphine equivalents; CDC has recommended that we stay at 50 morphine equivalents per day or less for chronic therapy for most patients with chronic pain; if patients become tolerant to those drugs, do not continue to go up, because there is no evidence of efficacy in most cases; 90 morphine equivalents per day is the maximum dose we should use in all cases except for terminal illness; no evidence going above 90 morphine equivalents per day improves efficacy

Hyperalgesia: means going above 90 mg of morphine equivalents per day could make a person's pain worse instead of better; thought to be a receptor phenomenon; high-dose opioid patients appear to have worse outcomes with neuromodulation in a recent Medicare analysis published in the *Journal of Neuromodulation*

Other recommendations: important to make referrals to a pain specialist before someone is placed on high-dose opioids, because their chance of doing well is improved; opioids should be low in the algorithm; use only when other options fail; monitor closely with urine drug screening; patients should have frequent visits with the doctor or nurse practitioner to evaluate compliance and efficacy and, when appropriate, to have pill counts; reasonable to have them evaluated by psychology or addiction medicine if there are any questions about diversion or abuse of medication; in most cases, opioids can be avoided in chronic pain, and other interventions can be successful

Suggested Reading

Caes L et al: Current evidence-based interdisciplinary treatment options for pediatric musculoskeletal pain. *Curr Treatm Opt Rheumatol* 2018 4(3):223-34; **Cheatle MD:** Prescription opioid misuse, abuse, morbidity, and mortality: Balancing effective pain management and safety. *Pain Med* 2015 Oct;16 Suppl 1:S3-8; **Cooper TE et al:** Antidepressants for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst Rev* 2017 Aug 5;8:CD012535; **Deer TR et al:** The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* 2014 Aug;17(6):515-50; **Luthi F et al:** Avoidance, pacing, or persistence in multidisciplinary functional rehabilitation for chronic musculoskeletal pain: An observational study with cross-sectional and longitudinal analyses. *PLoS One* 2018 Sep 4; 13(9):e0203329; **Maher DP et al:** Neuropathic pain medication does not alter outcomes of spinal cord stimulation for lower extremity pain. *Neuromodulation* 2018 Jan; 21(1):106-13; **Guerriero F:** Guidance on opioids prescribing for the management of persistent non-cancer pain in older adults. *World J Clin Cases* 2017 Mar 16;5(3)73-81; **Prostran M et al:** Pharmacotherapy of pain in the older population: The place of opioids. *Front Aging Neurosci* 2016 Jun 16;8:144; **Shipton EA et al:** A review of the opioid epidemic: What do we do about it? *Pain Ther* 2018 Jun;7(1):23-36.

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Palliative Care

David Casarett, MD, *Chief of Palliative Medicine at Duke University, Durham, North Carolina; Professor of Medicine, Duke University College of Medicine, Durham, North Carolina*

Overview: three important aspects of palliative care are often underemphasized in clinical practice; these are communication and decision-making, pain management, and dyspnea management

Conversations

Representative case: MB is a sixty-three-year-old retired cartoonist with metastatic colon cancer that has progressed despite chemotherapy; has been hospitalized for 0 days with profound anemia requiring transfusions; patient has additional medical problems, including diabetes, coronary artery disease, and moderate renal insufficiency; he has new liver metastases, tumor size has doubled; the oncologist is convinced that there are no chemotherapy options that would offer any benefit and that patient wouldn't qualify for early-phase trials; a conversation with the hospitalist recommending cessation of chemotherapy and enrolling in hospice goes poorly; why?

Reasons for the outcome: these end-of-life discussions, or discussions about treatment, can be difficult; decision-making in these situations can be relatively straightforward, especially in the case of a patient with limited treatment options; implementing recommendations in a calm, sensitive, empathetic way can be difficult, especially when emotions run high; this is a matter of life and death; particularly difficult because healthcare providers do not get a lot of training on how to have these discussions in an effective, efficient, and compassionate way

When: discussions can happen at any point in a patient's illness trajectory; difficult conversations or goals-of-care conversations are often called end-of-life conversations but do not always take place at the end of life; might happen at diagnosis or when a patient is deciding on a major, life-defining treatment intervention like a bone marrow transplant or ventricular assist device implantation; sometimes the patient, such as one who is considering a bone marrow transplant, might have, with therapy, a long, healthy life; helps if we don't think of them as end-of-life discussions; think of them as difficult conversations that need a strategy

SPIKES strategy: created by Walter Baile more than 5 years ago; S stands for "set up"; P stands for "perception"; I stands for "invitation"; K stands for "knowledge"; E stands for responding to "emotion"; S stands for "summarizing"

Set-up: first step in SPIKES mnemonic; making sure the set up for a conversation is as good as it can possibly be; this can be difficult for busy clinicians; we do the best we can; making sure we have private space; minimizing interruptions; asking the patient who should be there; these could be other healthcare providers; in MB's case, might have helped to have the oncologist who had followed patient; these could be family members; can frame the question by saying, "We need to talk about how your treatment is going, what the next steps should be. This will be an important discussion. Who should be there with you or for you?"; sit down whenever possible; consider bringing own chair to avoid standing over patient; have a direct view of the patient; have tissue available, possibly bring some yourself; try to provide an environment, background, and tone that is unhurried

Perception: the second letter in SPIKES; find out what the patient and family know; find out perceptions or misperceptions about what's going on; general questions can be useful; ask what other doctors have said about why the patient is in hospital, about the treatment, about what is likely to happen, and about when the patient may go home; framing in that way, asking what people have told the patient, has several advantages; it makes the question less interrogatory, less threatening; useful because patients hear different things from different healthcare providers; helpful to know not just what a patient understands, but what they do not understand, how and why they are confused

Invitation: third letter in SPIKES; try as much as possible to ask for permission; ask if it is okay to talk about this and whether it is okay to talk about this now; make sure that the people in the room are the people who should be in the room; make sure that this is the best time for the patient to have this kind of discussion; for example, patient may just have woken up, just have taken pain medication, or just may not feel alert; try to arrange discussion and time on patient's terms so you have patient's permission for discussion

When the patient resists decision-making: sometimes patients do not want to make these decisions; this is unusual, but not unheard-of, and probably more common in some ethnic groups than others; if patient does not want to have the discussion, it is usually appropriate to honor that request and sometimes practically impossible to do anything else; if patients really do not want to hear us, they won't; when patients do not want to hear what we tell them, and do not want to be involved in the decision, it is important to clarify that specifically and to document it in the medical record; it can be useful to define parameters; you might explain that someone else, like a daughter, will make decisions if the patient does not want to do so; get patient's permission for this; can

give patient a choice between having someone else make the decisions or having that person talk to the physicians and then share information selectively with the patient; document conversations carefully, so it's clear in the medical record that you are respecting the patient's wishes; can be useful to revisit those decisions frequently because patients change their minds

Knowledge: the fourth letter in the SPIKES protocol; ask patients what they know, tell them, give them information, and then ask them another question or two to ensure that they understand the information; called ask-tell-ask; ask patients what they understand of what doctors have told them; eg, "why do you think you're feeling weak?";tell the patient, as clearly as you can, what you need to communicate; often useful to acknowledge what the patient has said; if you can, try to acknowledge the patient's own explanatory model and then modify that, build on it, and add to it; finally, ask the patient if he or she understands what you said, either in general terms, by asking whether what you said makes sense, or more directly by asking whether they think that what you said might be true

Emotion: the fifth letter in the SPIKES protocol, E for emotion, is responding to fears and concerns that these conversations often unearth; in general, best way to begin to respond to those emotions is simply to repeat what you are hearing, or what you think you are hearing; provides a chance both for us to begin to validate what patients are telling us, and also to confirm that what we are hearing is really what they are trying to tell us; more explicitly, it is useful to validate what we are hearing by saying something like, "I can't imagine how frightening it must be to feel like your strength is only going to decrease over time, that your strength is being limited by the cancer that's advancing"; you could also say that, "Many people in your circumstances would also be frightened by what they're seeing," as a way both of showing them you understand what they are saying, and of validating what they're concerned about; can put in the context of what you as a clinician know and understand, or what you think other patients like them would say

Reframing conversations: one challenge is the feeling that communicating openly and honestly about decisions regarding treatment or prognosis takes away hope; one way to deal with those concerns is to muscle through it, and to say to ourselves that it is a conversation that we have to have; we do need to have these conversations, even if they are difficult, but they do not have to be more difficult than necessary; they don't need to take away hope; there are proven ways of communicating even very bad news, while still communicating hope for the future; one way is to say that hoping for the best is useful and optimistic, and allows people to think in ideal ways about the future, but also allows them to prepare for the worst; it can also be useful to reframe what people are hoping for; maybe there are things that are achievable; sometimes those things are even goals that are more important to a patient; it can also be useful to talk about hope in personal terms; eg, "I hope that the weakness you're experiencing is temporary, but I'm afraid it may not be. If it isn't, are there other goals we might work toward?"; this is a framework that James Tulsky came up with, and I have personally found it very useful; it fits with the "hope for the best but prepare for the worst" principle; it also makes the issue more personal, by saying, "I'm hoping for this for you, but I'm afraid on your behalf that things might not work out as well as you'd hoped"; it's a way of demonstrating to the patient that, as healthcare providers, we have a personal investment in how things turn out for them, that we are hoping for them, and that we are afraid for them

Errors to avoid: empty reassurances do not help; many healthcare providers are tempted to offer various lines, words, and phrases ("Everything will work out"; "Let's take things one day at a time")to get out of the room quickly and to avoid an emotional conversation; these are easy ways out for a healthcare provider, but they are ultimately not helpful to the patient; they do not sound believable; the way to offer reassurance is to understand, empathize, and validate the patient's concerns

Summarize: the last letter in SPIKES; a way both of confirming to the patient that you have been listening, understanding, and appreciating what they have told you, as well as beginning to make some plans for the future; sometimes that is as simple as reframing, or even more simply, repeating what you have heard; for example, "I understand that you feel your weakness is a result of being in the hospital; I also understand that you know your cancer is very advanced. Maybe you do not want to make any big decisions today, but we can talk again;" it is a way both of wrapping up the conversation and of making plans for future conversations as you move the ball further down the field

Goals: helpful to see these conversations about goals as part of a process that is not always linear; sometimes the goals, problems, preferences, and questions that we walk into a room to help patients address are addressed, but are then replaced in that meeting, or in subsequent meetings, with other concerns; questions about chemotherapy turn into questions about tube feedings, which turn into questions about parenteral nutrition, which turn into questions about whether chemotherapy or transfusions could be available on an outpatient basis, and then back to the original questions about chemotherapy or tube feeding; it can be frustrating, but keep in mind that although some discussions lead to a decision and closure within five minutes, many take much, much longer

Follow-up on MB: A second conversation, with a more prepared clinician using the SPIKES model, elicited that MB was aware of the reality of his condition, that he primarily did not want to stay in the hospital or return to the hospital, and that he hoped to live until his granddaughter's graduation. He decided to stop chemotherapy, returned home, entered a home hospice program, attended the graduation, was not readmitted to the hospital, and died three months after the initial conversation

Summary: the most important part of education about palliative care conversations is practice; there are resources available online; ask for feedback from patients; look for other, more formal training; get advice from colleagues who do this well; this is a lifelong process of learning and improvement

Pain and Symptom Management

Overview of medications: one of the most difficult questions that we face in treating pain with opioids is

deciding which opioid to use; there are many medications for pain besides opioids, but I will focus on opioids

Types: morphine is widely available and inexpensive; hydromorphone tends to be more potent, which is not usually an advantage except if a patient is on large doses; oxycodone is widely used although it has gotten bad press recently for patients with advanced illnesses, particularly malignancies; fentanyl patches are convenient for patients who are nearing the end of life, who may not be able to take medications by mouth, or even sublingually; the difficulty with the fentanyl patch is that it takes effect slowly, and changes to the fentanyl patch dose also take a while to take effect, so it's not a good modality if you anticipate having to make rapid or frequent changes in dose; methadone suffers from some of the same limitations as fentanyl; difficult to titrate, can be potentially dangerous to increase, or even to start, if you're not familiar with it; has the advantage of being relatively inexpensive; available intravenously and orally; has very long duration of effect; particularly useful for neuropathic pain; meperidine (Demerol) shouldn't be used; still occasionally used in the post-surgical setting, and for a few very specific indications; the palliative care field has moved on to the other opioids mentioned

Choosing an opioid:

Administration route: in situations in which an intravenous or subcutaneous route is indicated, morphine, hydromorphone, or occasionally methadone is commonly used; morphine or transdermal fentanyl are used for transdermal or sublingual approaches; rectal administration is appropriate in limited circumstances, particularly for patients near the end of life, for whom IV access is not possible, oral administration is not desirable, and a PEG tube or other GI tube feeding route is not available; liquid formulations of methadone can be administered through a PEG tube; there are difficulties of dosing, particularly in older adults for whom the duration of effect can be significantly longer than the half-life; leads to potential problems with sedation or confusion if patients aren't monitored; subcutaneous administration can be useful, particularly in the home setting; for most systems, the subcutaneous morphine limit is about 30 milligrams per hour; for patients who need more, particularly in a monitored home setting, a switch to hydromorphone can offer better pain relief with the same or a smaller volume; in general, subcutaneous opioids can be administered using a butterfly needle that can be changed every couple of days; medication is usually diluted in D5W (5% dextrose in water)

Neuropathic pain: another difficult situation in which one opioid may be significantly better than another; traditional opioids like morphine generally offer moderate effectiveness for neuropathic pain; growing data support the effectiveness of less selective agents; levorphanol is sometimes used; data are strongest for touch-induced allodynia and peripheral neuropathy

Methadone: this has gotten increased attention because of its actions on NMDA (N-methyl-D-aspartate) receptors and the way that it inhibits norepinephrine and serotonin reuptake; it can be administered by IV or, more commonly, in an oral form

Hepatic failure: opioid metabolism generally takes place in the liver, including conjugation for some drugs; some drugs, specifically methadone and codeine, generally should be avoided in liver failure; oxycodone, morphine, hydromorphone, and fentanyl are preferable

Renal failure: try to avoid agents that have significant renal clearance, like oxycodone and methadone, though low-dose methadone can sometimes be used; try to select agents with inactive metabolites, like fentanyl or hydromorphone

Dyspnea

Overview: can be very distressing for patients, healthcare providers, and family members; while the differential diagnosis of pain has a relatively limited effect on the choice of pain treatments, apart from decisions about whether pain is neuropathic or not, the etiology of dyspnea, particularly in the setting of malignancy, can lead to very different approaches to pain management; for instance, pleural disease, or pleural fluid, often responds to a tap; on the other hand, conditions like anemia or chemotherapy toxicity, or underlying diseases like COPD (chronic obstructive pulmonary disease) or CHF (congestive heart failure), might be treated in different ways both symptomatically and with respect to the treatment of the primary condition

Modalities used: five or six modalities are used most commonly; the data are strong for opioids; the data are slightly less strong for non-pharmacologic interventions (one of the most common is the use of a fan blowing on the patient's face); other analgesics or benzodiazepines have less data to support them; oxygen has strong data supporting it, particularly for those patients with reduced pO_2 (partial pressure of oxygen); the combination of oxygen and opioids is recommended as first line therapy for dyspnea, particularly in the setting of malignancy; the data indicate that oral and either IV or subcutaneous routes are equally effective, with doses similar to those of IV opioids for pain management; there is more limited data supporting nebulized opioids, so an oral or an IV route is generally preferred

Summary Recommendations

Keep up with the literature; consult palliative care team; pay attention to the specific circumstances of the individual patient

Suggested Reading

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Geriatrics

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Introduction: geriatric assessment; 3 important geriatric conditions (falls, polypharmacy, urinary incontinence); pressure ulcers; driving assessment; care planning

Geriatrician: American Geriatrics Society (AGS) still considers what proper role of geriatrician should be; at one point, no geriatricians in the United States (US); at that time, all primary care doctors "undocumented geriatricians," but population of older people in US was smaller in both absolute and relative numbers

Aging statistics: society aging; population of older adults, currently ~40 million, will double by 2050; result, too few geriatricians to care for all elderly people, as pediatricians might care for their patients; about to enter phase when persons aged ≥85 yrs fastest-growing segment of population

Geriatrician statistics: in 2015, AGS counted 7500 geriatricians per 12 million older adults; at that time, estimated 17,000 geriatricians needed; demonstrates 1:1 model of care for patients insufficient, and geriatricians need to be need to be primary care doctors (and also consultants and advocates); internists, family practitioners, and especially doctors in hospital setting need to recognize that they comprise part of today's "undocumented geriatrician" workforce

Hospitalization: by 2008, 40% of hospitalized patients were aged >65 yrs and 9.2% of hospital discharges patients aged >85 yrs (representing greater proportion of hospital patients than their proportion in population because of longer average length of hospital stay because of vulnerabilities and complications in hospital

Advocacy role: another role for geriatricians; must promote healthy aging to allow for longevity in any case (read white paper on healthy aging published in *Journal of the American Geriatrics Society* [*JAGS*] listed in suggested reading)

Diseases of geriatric patients: geriatricians must specifically focus on geriatric diseases in elderly patients; these include urinary incontinence, dementia, gait impairment, delirium, multisensory deficit (involving vision, hearing, and proprioception); these conditions often multifactorial, chronic, and coexisting

Themes in geriatrics: *multimorbidity* — entails managing 1 disease in context of several diseases; *frailty* — poorly defined but very real; affects some, but not all, elderly individual; frailty associated with sarcopenia (condition in which muscle mass gradually replaced by adipose tissue, with implications in muscle strength and endurance)

Recommendations for geriatric patients: discovery in recent years that regular exercise and Mediterranean diet or plant-based diet can reduce risks of cognitive impairment and frailty, even when commenced in older age; brings to mind advice from Jane Fonda in 1982 when she said, "eat right and stay fit" (we now know better what that means)

Complexity: multimorbidity involves complexity; tautology, "knowing one complex individual requires individualization of all patients"; quote from Dr. Francis Peabody (1925 Harvard lecture), "for the secret of care of the patient is in caring for the patient" (*ie*, fully understanding patient)

Teamwork: need for geriatricians to work on teams, another implication of complexity; geriatricians recognize crucial to be aware of nonmedical determinants of health and not enough to manage only medical illness; another quote by William Osler, "it is more important to know what sort of patient has the disease than what sort of disease the patient has"; emphasis of quote, knowing patient in holistic and more intimate way

Defined goals: need to define goals for patient in context of illness and diminishing life expectancy additional feature of complexity

Geriatric Assessment

Overview: popular term meaning opportunity to find ways to benefit older patients by taking comprehensive approach; involves several domains

Hearing and vision: measured in order to understand the possibility of multisensory deficits that often cause isolation in older adults

Function: older adults sometimes more concerned with function than with actual cure of chronic diseases; Functional Activities Questionnaire (FAQ) 1 way to measure function; FAQ found online and administered by office staff (physician's time not hindered)

Gait: evaluate gait of older patient; assessed quickly with Timed Up and Go (TUG) test

Incontinence: often not reported by patient, but incontinence quite prevalent, particularly in women; parallels onset of impaired cognition; increases with age; by age 80 yrs or mid-80s, many individuals have both incontinence and dementia, at about same prevalence of (~35%-40%)

Depression: best evaluated using validated instruments; geriatricians favor Geriatric Depression Scale (GDS) by Yesavage, which has little dependence on individual's memory; simple "yes/no" answers with only short contemplation needed by adult, so quick test; often, patients responding to questions discover gravity of their

condition on their own and begin to think of ways to improve life

Cognition: validated instruments for screening and scoring cognitive impairment only part of diagnostic criteria for dementia (dementia also implies functional impairment interfering with performance of daily tasks and social impairment); annual Medicare wellness visit entails assessment of cognitive function, but does not specify which assessment; US Preventive Services Task Force has failed to endorse screening for dementia, partly because their evaluation shows scant evidence of value of cognition-enhancing medicines; however, most geriatricians believe, if not screening for dementia, to at least ask key questions because of important role of counseling (even in absence of a truly effective treatment for dementia)

Pharmacy: essential to review (perhaps, with assistance of pharmacist) patient's prescribed medications, as well as alcohol, opioids, and over-the-counter medicines

Review of systems: do not omit questions about nutrition, insomnia, and advanced care planning; *reminder*- problems with vision, cognition, and neuromuscular function may translate into an incapacity of older patient to drive safely, which may lead to need for further driving assessment

Falls and Fall Prevention

Overview: important to address with elderly patients; geriatricians typically state that falls do not occur as result of accident; epidemiology of falling and predictive factors in falling can be addressed; falls widespread; one-third of persons aged >85 yrs fall annually, with 20% to 30% of falls resulting in injury

Scenario: imagine patient on panel that includes married couple in their 80s, Mr and Mrs V (*V* as in vulnerable or venerable); Mr V taught high school and coached track; Mrs V raised their children, and later worked part-time as clerk in clothing store; both have been patients for many years, ostensibly in good health; Mr V reports that his wife has fallen twice in previous 3 mos to 4 mos for no apparent reason; knowing that she, being aged >65 yrs, at some risk of falling; history of 2 falls increases her risk for additional falls

Fall intervention: *how do you evaluate causes and prevent falls, or find proper intervention?* — according to US Preventive Services Task Force, for individuals at increased risk of falling, consider recommending exercise (grade B recommendation) or physical therapy (grade C recommendation); Task Force neither defines increased risk nor specifies details of either exercise or physical therapy; *reminder*- in formal structured process, US Preventive Services Task Force uses strict logic to review medical literature in valid clinical trials for evidence of favorable effects, which sets high bar; with respect to falls in Mr and Mrs V's case, hindered by many endpoints used in clinical trials (number of falls, number of persons falling, falls with injury, falls with fracture, heterogeneity of different interventions); many endpoints makes comparing results from nonuniform trials using meta-analysis very difficult

Vitamin D: previously, US Preventive Services Task Force recommended vitamin D in asymptomatic community dwellers; recommendation dropped because of inconsistency in earlier trials regarding if supplementation based on low serum levels of vitamin D; ≥1 trial associated vitamin D supplement with harm

Statins: in primary prevention in individuals aged >79 yrs, US Preventive Services Task Force recommendations for statin use 30% across the US; for secondary prevention, 50%; for individuals aged ≥79 yrs, very little evidence of value of statins in primary prevention; not surprising, since patients in nursing homes and hospitals have very long medicine lists

Deprescribing

Beers list: Mark Beers, physician who created list in 1991 of what he called "potentially inappropriate" medicines for older individuals; after his death, AGS finished list and was assigned to review and update it in 2011; AGS undertook formal, structured literature review with stakeholder input and expert consensus; last review 2018, but last published review 2015 in *JAGS*

Deprescribing: 2015 Updated Beers Criteria review reveals potential drugs with greatest degree of side effects and adverse effects in elderly individuals; contains reference tables to help in drug review in interest of deprescribing; physician can deprescribe in any practice setting (*eg*, hospital, residential facility, office)

Algorithms: include algorithm published by Garfinkel 10 yrs ago; logic of algorithms simple, starting with question, "Are you willing to try reducing?" directed to patient; many patients grateful for chance to eliminate medicines; question patients about side effects; virtually any symptom can be drug related, especially in older adults who may have anorexia, weight loss, confusion, syncope, falling, gastrointestinal problems, and edema (these particular side effects often not reported by patients unless specifically questioned)

Process: ask if specific medicine still needed, if duplicate medications; consider patient's life expectancy compared with time to benefit (*eg*, think about Mrs V and bisphosphonates); if medicine cannot be fully deprescribed, think about tapering or lowering dose; consider reducing pill burden (connected to quality of life [QoL]), particularly for patients who may have difficulty swallowing medicines; consider choosing drug with fewer side effects; consider using stepwise approach, which means not completing deprescribing task in single visit, but take iterative approach over course of many visits

Lack of deprescribing: why aren't we doing more deprescribing?; obvious answers to this question, but question has been studied; *answers from study at US Department of Veterans Affairs* — too little time to talk with patient; easier to prescribe than to say, "Why not?"; physicians' presumptions made about patients' dependence on medicines; physicians afraid of violating guidelines and suffering penalties or negative profiling if medicine indicated for specific condition honored by guideline; fear of liability (implies that all matters must be discussed with patients); lack of consensus among prescribers leading to hesitation to discontinue drug of another doctor has ordered

Pharmacist: one recommendation to emphasize, seek help from pharmacist, expert in drugs and side effects; can be very helpful collaborators; get to know pharmacist and establish some understanding about values of deprescribing

Article: article by Hannah Dills (*Journal of the American Medical Directors Association*) evaluated >50 deprescribing trials, not restricted to elderly in this case; discovered that ~20% required resumption of antidepressants; implies that geriatricians must monitor patient when discontinuing medicine; restarting medicine may be needed, but does not negate value of deprescribing for many patients able to discontinue medicines

Urinary Incontinence

Overview: prevalence of urinary incontinence similar to cognitive impairment in older adults; increases with age; can have significant impact on lifestyle (may take people out of workplace and prevent engagement in social activities)

Sources of incontinence (simplified): stress incontinence, urge incontinence, and combination of stress and urge incontinence; stress urinary incontinence occurs with laughing or coughing, related to intraabdominal pressure overcoming resistance from pelvic floor muscles; urge incontinence (overactive bladder) refers to decreased time to bathroom; related to spastic or twitchy detrusor muscle; some individuals have combinations of stress and urge incontinence

Treatment: *important*- high-value care now proposes muscle training rather than medicines as first-line treatment for incontinence; pelvic floor training (Kegel exercises) for stress incontinence, bladder training for urge incontinence; muscle training recommended over drugs partly because many drugs do not have benefits over muscle training and have little benefit over placebo; additionally, anticholinergic properties of overactive bladder medicines pose the risk of central nervous system side effects

Relation to medicines: incontinence possibility related to medicine; nocturia and functional incontinence can be caused by redistribution of edema related to diuretics; also may be urinary retention with overflow incontinence related to medicines such as opioids or anticholinergics

Driving Assessment

Overview: motor vehicle accidents third-leading cause of accident injury in US; on average, life expectancy for older adults exceeds driving fitness expectancy (gap 6 yrs for men, 10 yrs for women); most older adults will need to retire from driving at some point during lifetime; central part of aging and should be determined when to give up driver's license

Obligation of clinician: both public safety and patient, but should not be dichotomous goals; although younger drivers have more accidents per capita, older drivers (aged >75 yrs for males and >60 yrs for females) have higher death rates per capita (meaning definite risk for drivers who are no longer safe drivers); if primary care provider advised to stop driving, most older adults agree that they would discontinue driving (but testable hypothesis); as their skills decline, older drivers tend to rate their driving as better than it actually is, so input necessary; skills decline, so need input

Legal requirements: differ from state to state; information available from websites sponsored by Department of Motor Vehicles or Department of Transportation for the state, National Highway Traffic Safety Agency, sometimes the American Automobile Association; some states have mandatory reporting in which violation of that reporting requirement may entail physician liability for failure to report

Scenario: on annual exam, Mr V scores in mild cognitive impairment range on Montreal Cognitive Assessment Test (MoCA) testing; Mrs V confidentially discusses concerns about Mr V's driving (distractible and reaction time seems like what it should be); what should clinician do?

Assessment: no single validated screening tool to assess driving safety; almost all cases need multifaceted approach; TUG test, useful for evaluating gait, not reliable indicator of driving safety; related test, Rapid Pace Walk test, involves simply walking 10 ft back and forth at rapid pace; time to walk >9 secs suggests association with driving impairment (Rapid Pace Walk test may be good office screening test)

Familial input: when assessing driving safety, most important recommendation, gathering information and eliciting collaboration from families in decision of when to voluntarily give up driving; formal way, completing form and submitted to Motor Vehicle Division; for state's driving safety and requirements, important to refer to websites of National Highway Traffic Safety Agency, local aging and disability services, and National Occupational Therapy Group

Pressure Ulcers

Overview: classification of ulcers by type; pressure ulcers one of multiple types of ulcers, distinguished from arterial ulcers, diabetic ulcers, and venous ulcers; other ulcers not staged in same way as pressure ulcers; staging for pressure ulcers does not apply to burns, traumatic wounds, adhesive-tape injury, diaper rash, and dermatitis

Staging: staging not tantamount to measured depth of ulcer, but to extent of penetration through anatomic layers; national updated staging system approved by National Pressure Ulcer Advisory Panel

Stage 4: reverse order easiest way to remember staging, remembering that stage 4 ulcers reach through skin and adipose tissue to fascia, tendon, muscle, or bone; therefore, if any of those structures visible in wound, pressure ulcer stage 4

Stage 3: ulcer goes through skin to adipose tissue, but often presence of granulation and sometimes tunneling; called full-thickness ulcer

Stage 2: ulcer goes through epidermis to red, viable dermis with no granulation; *eg*, applies to blister whether roofed or unroofed; called partial-thickness ulcer

Stage 1: ulcer on intact skin with nonblanchable erythema; may question presence of ulcer

Unstageable: level of penetration concealed by eschar (slough); unstageable wounds may exist at bone-muscle interface with overlying skin intact; surface may have purplish discoloration

Treatment: remove debris, remove necrotic tissue, pack dead space, and control bacteria

Prevention: mainly good nursing; entails reducing shear, unweighting, and repositioning areas of bony prominence; promoting perfusion to the area; keeping wet skin dry and overly dry skin lubricated; *reminder*- early detection to spur treatment can prevent ulcers from worsening

Care Planning

Overview: theme for geriatricians taking care of older adults; individuals like Mr and Mrs V may have very different perception of their QoL than might have been defined for them by researchers or demographers; patients can be highly satisfied with QoL that researchers would consider low

Goals: according to surveys and patients themselves, patients may not emphasize longevity as most important or cherished goal, but rather emphasize retaining functional status and independence, and not being burden to others; patients can be resourceful in adapting to change brought about by new condition, illness, or injury; goals of patients change, not only over yrs, but very abruptly with onset of illness

Visit: understand patient preferences without having full discussion; can be part of annual Medicare wellness visit (compensated and coded separately); important to document and include changes over time

Conclusion

Important points: 1. aging population makes all doctors (especially hospitalists) who treat adult patients "undocumented geriatricians"; 2. look for opportunities to deprescribe or, at least as AGS urges, think twice and review carefully before prescribing additional medicine to older adult; 3. remember that falls not accidents; they have predictors; individuals who fall at risk of falling again; studies have shown effectiveness and cost-effectiveness of specific interventions; 4. learn and accommodate changing treatment goals for aging patients (important part of holistic care)

Suggested Reading

American Geriatrics Society 2015 Beers Criteria Update Expert Panel: American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2015;63(11):2227-46; **Dills H et al:** Deprescribing medications for chronic diseases management in primary care settings: a systematic review of randomized controlled trials. *J Am Med Dir Assoc*. 2018;19(11):923-35.e2; **Friedman SM et al:** Healthy aging: American Geriatrics Society white paper executive summary. *J Am Geriatr Soc*. 2019;67(1):17-20; **Mielenz TJ et al:** Select physical performance measures and driving outcomes in older adults. *Inj Epidemiol*. 2017;4(1):14; **National Pressure Ulcer Advisory Panel** (NPUAP): NPUAP Pressure Injury Stages. NPUAP 2016 Staging Consensus Conference. April 8-9, 2016; Chicago, IL; **Scotti S:** Preventing elderly falls. *NCSL Legisbrief*. 2016;24(17):1-2; **Suskind AM et al:** A screening tool for clinically relevant urinary incontinence. *Neurourol Urodyn*. 2015;34(4):332-5.

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Eye Diseases for the Internist

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Approach to the Red Eye

Layers of eye surface:

Tear film: 3 layers; lipid outermost layer formed by Meibomian glands (within tarsal plate of eyelids), seals tears in; water component formed by lacrimal and accessory lacrimal glands (superotemporal); mucin layer formed by goblet cells to help tear film stick to eye; eyelids mix tear film into layers; blinking dissipates and reforms tear film; provides refractive surface and fights infection

Conjunctiva: flimsy tissue; covers white part of eye and lines innermost part of eyelids; bulbar conjunctiva covers white part of eye; palpebral conjunctiva lines eyelids; conjunctiva meets cornea at limbus; beneath conjunctiva are episclera and sclera; episclera has layer of blood vessels above white of eye; sclera has superficial blood vessels but avascular at deeper level

Red eye: consider layers from outside to inside

Ocular surface disease: disorders of tear film and superficial cornea; look for skin changes around eye (rosacea, seborrheic dermatitis), eyelid function; in ectropion, eyelid flapping out; in entropion, eyelid twisted in; look for laxity (common in sleep apnea); slit-lamp examination of lid margin for signs of blepharitis; anterior blepharitis has crust or collarette on lashes and eyes that causes red and scratchy eye; posterior blepharitis (Meibomian gland dysfunction) involves sebaceous glands in tarsal plate of conjunctiva and causes tears not to last long; anatomic disorders can cause tear film problems; conjunctivochalasis is degenerative change causing conjunctiva to become loose and drape over lower eyelid; check with slit-lamp and fluorescein strip; growths on eye can block flow of tears; pterygium is a common wing-like growth over cornea that is benign and related to sun exposure, can decrease vision if blocks pupil or cause astigmatism; should be examined to rule out malignancy

Subconjunctival hemorrhage: diffuse bleeding; dramatic but benign and resolves on its own; check blood pressure; usually does not progress; patients on blood thinners or who have had recent trauma or rubbing of eye are at risk

Bump on upper cornea: filtering surgery for glaucoma causes bleb or bump on top part of cornea; sometimes misdiagnosed as ocular problem but it is iatrogenic

Cornea: look for scratch with or without stain; epithelial erosion (punctate epithelial erosion) or corneal abrasion (missing epithelium); assess tear layer with blink and time how long tears last; look for dryness

Aqueous tear deficiency: ocular surface disorder; dry eye from insufficient tear production; associated with a lot of corneal staining or epithelial disruption and low tear lake; in young patient, ask about dry mouth because tear deficiency associated with Sjogren's; in general with eye disorders, important to determine whether localized or related to systemic disorder; consider graft versus host disease

Limbus: area where bulbar conjunctiva meets cornea; epithelial limbal stem cells responsible for keeping corneal epithelium clear and their absence results in conjunctiva overgrowing cornea to cause limbal stem cell deficiency; common causes are chemical burn or trauma; medical emergency that requires immediate eye flushing until pH normalizes (use strips); if pH does not normalize, particulate matter may need to be removed from under eyelid using irrigation (have patient look down and flip lid); examine ocular surface to assess damage; limbal ischemia (whiteness around limbus) indicates damage to limbal stem cells and limbal stem cell deficiency likely; red limbus is good sign that enough cells present to respond to injury; start topical antibiotic to minimize infection risk; consider topical prednisolone to decrease inflammation; cover with bandage contact lens or amniotic membrane covered by contact lens to decrease inflammation and make more hospitable environment on ocular surface; may give oral vitamin C to help with wound healing and oral doxycycline to decrease MMP9 (matrix metallopeptidase 9) levels; follow patient closely to monitor for infection and evaluate healing; main prognostic factor for healing after chemical burn is whether residual limbal stem cells present to repopulate corneal epithelium; vision suffers without a clear cornea

Conjunctivitis: inflammation of palpebral conjunctiva; normal conjunctiva pink with underlying straight blood vessels; in conjunctivitis, lining replaced by bumps (follicular conjunctivitis) of aggregated lymphocytes, papillae (fibrovascular bundles with blood vessels), or scarring; papillae any size; acute (less than 6 weeks) or chronic

Acute follicular conjunctivitis (adenoviral conjunctivitis): 2-3 days of watery red eye; bumps on conjunctiva with few papillae; some strains cause very severe disease with pseudomembranes on inner lining that appear white and milky and stuck to palpebral conjunctiva, require peeling to prevent permanent scarring; preauricular node not necessary to diagnose; 2 weeks after infection resolves, some patients have immune response manifest as little dots under corneal epithelium (subepithelial infiltrates), which can be chronic; treat with topical steroids (responsive but may recur); dots affect vision and cause light sensitivity; disease affects younger patients and severe disease can cause residual scarring and prolonged subepithelial

infiltrates; treat with artificial tears; very contagious; patients should not touch eye or share towels; wash sheets and towels; usually bilateral but avoid touching other eye if unilateral; patients should not go to work; if patient requires membrane removal, start topical corticosteroid; recognize when membrane peels necessary versus conservative therapy

Acute papillary conjunctivitis: most commonly associated with bacterial infection; generally self-limited because most bacteria unable to penetrate intact epithelium; differentiate from viral conjunctivitis by looking at reaction of conjunctiva (follicles more common with virus and papillae more common with bacteria) and secretion type (viral is serosanguinous and bacterial has pus)

Gonococcal conjunctivitis: presents as hyper-acute conjunctivitis; copious pus; if untreated, can penetrate intact corneal epithelium and progress to corneal ulcer and perforation; treat aggressively and treat partners for this and chlamydia

Chronic follicular conjunctivitis: months of scant discharge, itching, burning; inferior conjunctival bumps/follicles; differential diagnosis — chlamydia conjunctivitis (serotypes D through K, sexually transmitted disease) does not cause scarring or vision loss; molluscum contagiosum of eyelid, lymphoma, and chlamydia trachoma (serotypes A to C) also cause follicular conjunctivitis

Trachoma: presents as cicatricial conjunctivitis of upper eyelid outside US where endemic; scarring noted when lids are flipped; causes so much morbidity because we blink many times a day and is like sandpaper continually scratching cornea and limbal stem cells; limbal stem cell deficiency results when there is corneal scarring and loss of limbal stem cells; causes vision loss

Molluscum contagiosum: eyelids; sometimes underneath inferior eyelash line and missed; presence should cause consideration of immunosuppression like HIV (more commonly associated with CMV retinitis)

Herpetic (HSV 1) disease: acute follicular or papillary conjunctivitis with vesicles on eyelid; primary presentation is blepharoconjunctivitis; skin lesion may be very subtle (pimple that resolves and people do not realize it is herpes); HSV resides within trigeminal ganglion; reactivation leads to many possible presentations; classic lesion is epithelial defect shaped like a flower (dendrite); treat with topical or oral antivirals to shorten disease course from 10 to 14 days to 7 to 10 days to minimize scarring; after dendrite resolves, HSV can cause interstitial keratitis (inflammation and scarring in corneal stroma); can cause endothelial disease; endothelial cells are pump cells of cornea and when inflamed, corneal edema results; HSV can cause inflammation inside eye; inflammation in anterior chamber is anterior chamber uveitis or iritis; HSV can enter drainage system and elevate pressure; HSV can infect retina and cause retinitis; HSV should be in differential for any eye disease presentation

Varicella-zoster virus (VZV): higher risk of eye disease if involves V1 distribution of trigeminal nerve; eye disease appears 1 to 4 weeks after rash; need to monitor for 1 month for eye complications; 50% of patients with V1 zoster (forehead, eye, and tip of nose) eventually develop eye disease; eye disease can involve corneal changes like pseudodendrites (heaped up pieces of mucous and inflammatory cells stuck to eye); can cause inflammation of anterior segment (iritis) or retinitis (rarer but more morbid); advocate for vaccination for all patients; treat VZV with 10 to 14 days of valaciclovir 1 g three times a day; if chronic or recurrent, consider suppressive therapy with 1 g once per day; many eye sequelae caused by immune response; patients with anterior chamber inflammation (iritis) require prolonged low-dose topical corticosteroids

Allergic acute or chronic papillary conjunctivitis: seasonal allergies do not affect vision

Vernal conjunctivitis: large papillae on upper palpebral conjunctiva (like trachoma); papillae rub against cornea and cause shield ulcers and vision loss; more common in children; treat acutely with topical prednisolone; to prevent onset of vernal conjunctivitis, pretreat with antihistamine and mast-cell inhibitor; most kids outgrow but important to maintain vision; treat with antihistamines and mast cell inhibitors

Perennial allergies: atopic keratoconjunctivitis; T-cell mediated and treated with t-cell inhibitors (tacrolimus ointment or oral t-cell mediators like cyclosporine and tacrolimus)

Cicatricial conjunctivitis: scarring in eyelids; may result from severe adenoviral infection; consider mucous membrane pemphigoid in older patient with waxing and waning course; diagnose with biopsy and immunohistochemistry to look for positions of immunoglobulins and complement in basement membrane; subcategorize using antigen and staining pattern; this systemic disease requires systemic treatment to prevent blindness; often diagnosed by ophthalmologist or dentist

Conjunctival granulomas: due to sarcoidosis, lymphoma, or mucous membrane pemphigoid; can be easily biopsied

Episcleritis: bulbar injection without palpebral changes (if palpebral changes present, it's conjunctivitis); usually due to ocular surface conditions like dry eye and blepharitis; worrisome if bilateral or persistent because can be associated with systemic inflammatory diseases; need to differentiate episcleritis (superficial vessel inflammation, not painful) from scleritis (involves deeper vessels, painful, and more serious); redness in episcleritis superficial (can see redness in linear blood vessels) vs scleritis has deeper redness with purple hue; redness is mobile in episcleritis (use a Q-Tip to test), immobile in scleritis; phenylephrine removes redness in episcleritis but not scleritis

Scleritis: 50% have underlying etiology; commonly associated with systemic autoimmune disease (rheumatoid arthritis, vasculitis, relapsing polychondritis); most common autoimmune comorbidity is rheumatoid arthritis (because rheumatoid arthritis very common; 33% of patients have scleritis); 50% of patients with vasculitis (especially granulomatosis with polyangiitis — formerly known as Wegener's disease) have scleritis; examine joints and check complete blood count (CBC), comprehensive metabolic panel (CMP), inflammatory disease markers (c-ANCA [cytoplasmic antineutrophil cytoplasmic antibody}, p-ANCA [perinuclear antineutrophil cytoplasmic antibody]), chest x-ray, urinalysis to look for end-organ damage; in vasculitis, look for hematuria with red blood cell casts; rule out infection with immune response, especially syphilis, tuberculosis (TB), Lyme disease

Diffuse anterior scleritis: most common type; redness is in anterior component (can see it and it is flat)
Nodular scleritis: has nodules
Necrotizing scleritis: white component that indicates necrosis within the redness and is an emergency — eyeball is melting; results from bacterial, viral, or fungal infection, so cultures essential; may also result from severe inflammatory disorder (vasculitis); treat inflammatory cases with systemic immunosuppressive therapy (oral prednisone); for some forms of mild scleritis can use high-dose NSAIDs (non-steroidal anti-inflammatory drugs) (ibuprofen 800 mg TID or naproxen 500 mg BID); NSAIDs cannot be used in patients with necrotizing disease; treat patients with systemic immune issues like rheumatoid arthritis with oral prednisone
Posterior scleritis: occasional presentation; redness not visible but ultrasound shows inflamed, thickened, choroid and sclera on B-scan
Scleromalacia perforans: very rare; seen in patients with long-standing, untreated rheumatoid arthritis; rarely seen now with new disease modifying agents; presents as scleral melt without inflammation; can see blue underlying choroid because sclera melted slowly over time

Keratitis: inflammation of cornea
Corneal ulcer: most common; can be caused by bacteria, viruses, acanthamoebae, fungi; cannot always tell what is causing by inspection; need culture and targeted therapy; most bacterial, so start with broad-spectrum antibiotics, refine treatment based on culture results; for fungal ulcer, start with natamycin (only commercially available agent); if need another antifungal, compound amphotericin or voriconazole; acanthamoeba more severe and difficult to treat; often delayed diagnosis and no specific anti-acanthamoebal agent; use general toxins like PHMB (polyhexamethylene biguanide, a pool cleaner); not very comfortable; patients who wear soft contact lenses and come in contact with contaminated water (eg, pond water) at risk
Peripheral corneal ulcer (peripheral ulcerative keratitis): can result from infection or autoimmune disease (rheumatoid arthritis, vasculitis)
Other causes of corneal ulcer or abrasion: neurotrophic etiologies, diabetes, lesion to trigeminal system; patients with history of zoster have decreased sensation, so epithelium breaks down and does not re-heal; if only epithelium involved, is called corneal epithelial defect; neurotrophic ulcers involve stroma and epithelium
Work up for corneal ulcer: rule out infection; systemic work up; differentiate from corneal abrasions with fluorescein to stain abrasion; see if underlying infiltrate present to differentiate traumatic but not infected from infected abrasion needing antibiotics; treat with scaffolding for neurotrophic epithelium to heal with bandage contact lens or amniotic membrane for inflammation; use newly approved treatment nerve growth factor (very expensive) when neurotrophic corneal epithelium does not heal

Iritis: very hard to see white blood cells floating in anterior chamber (hallmark of iritis) without slit-lamp; certain features can be seen with penlight to suggest iritis, anterior segment inflammation, or history of anterior segment inflammation; posterior synechia is scarring of iris to lens, causes irregular pupil; irregular pupil indicates possible eye inflammation, but also can be caused by trauma; cornea can be hazy; keratic precipitates are small dots in innermost cornea (white blood cells stuck to cornea) that cause haziness, indicate anterior chamber inflammation
Differential diagnosis of acute anterior chamber inflammation: systemic inflammatory disease (most common is HLA-B27-associated); ask about ankylosing spondylitis, psoriasis, and inflammatory bowel disease symptoms; also caused by infections and other inflammations; limited work up with HLA-B27, syphilis testing, and chest x-ray looking for sarcoid; sarcoid presents with acute anterior segment inflammation, red eye and anterior segment cell or more insidiously with white eye, no symptoms, and cells on examination; HLA-B27 disease commonly presents with acute red eye, photophobia, and cells inside eye

Glaucoma:
Closed angle glaucoma: has red eye; patients have narrow angles between iris and cornea and pupil dilates; angle may shut and pressure increase rapidly (from 15 to 60 mm Hg); very painful; anterior chamber will be very shallow; pupil may be stuck and not very resposive (partially dilated); if no Tono-Pen or other way to check pressure, have patient close eyes and touch 2 fingers back and forth over eyeball to press down; if you cannot indent globe, pressure is very elevated; globe should feel like tip of nose; ophthalmic exam necessary if worried about closed angle glaucoma because long-term high pressure damages optic nerve and must be lowered as quickly as possible with drops and laser; more common in Asians
Open angle glaucoma: most common type; pressure too high for optic nerve; some people have nerve damage at pressures of 12 mm Hg, and others not until pressures of 25 mm Hg; normal pressure usually 12 to 21 mm Hg; nerve damage at lower pressures is normotensive glaucoma; nerve damage at higher pressure is traditional open angle glaucoma
Evaluation and treatment: pressure is only modifiable risk; goal to lower pressure with drops, laser, or surgery; genetic and environmental components; many patients have family history; more severe in blacks than whites
Differential for red eye: orbit is area behind globe; any orbital process around muscles or optic nerve can cause venous congestion, redness, and proptosis; causes are vascular abnormality, tumor, infectious infiltrate; thyroid eye; look for restricted eye movement, proptosis, redness; use imaging (ultrasonography, CT) to identify; cavernous carotid fistula after trauma

Emergency indicators: red eye with pain, vision loss, history of recent surgery, or eye looks funny

Dry eye: misnomer; in Sjogren's, people actually have dry eyes because do not make enough tears, inflammation causes scratchiness of cornea and damaged epithelium, which is seen with fluorescein, often accompanied by dry mouth; most people who say their eyes feel dry do not have aqueous tear deficiency; a complaint of dry eye is an umbrella term for dry eye symptoms and signs; symptoms are generally sensations; patients complain about eyes feeling dry, burning, and aching and about visual quality; if vision is clear after blinking but becomes blurry until re-blinking, indicates unstable tear film; many different dry eye signs that can accompany

these symptoms like inadequate tear production, fast tear evaporation, inflammation, high osmolarity

Aqueous tear deficiency: actual dryness; measure with strips of paper to measure tear production or use slit-lamp to look at tear lake; deficiency associated with Sjogren's, graft versus host disease, and other autoimmune conditions

Meibomian gland dysfunction: contributing factors are age (both lacrimal and Meibomian gland production decline with age), rosacea or any skin condition; look for anatomical issues like conjunctivochalasis, glaucoma surgery, pterygium that impacts tear mixing on ocular surface; nerve dysfunction — some patients with fibromyalgia or other chronic pain conditions

Treatment: anti-inflammatory agents; T-cell inhibitors; topical cyclosporine; lifitegrast is a drug which inhibits integrin and lymphocyte function-associated antigen 1 (LFA 1) from binding to ICAM-1 (intercellular adhesion molecule 1); effect is to block T-cells; blocking T-cells is commonly used in patients with dry eye and inflammatory component (Sjogren's or graft versus host disease); if symptoms of dryness driven by lid disease, improve Meibomian gland function with lid hygiene; heat Meibomian glands to unblock openings on eyelid margin; decrease inflammation and improve oil quality by giving antibiotics (doxycycline); lasers to improve Meibomian gland health; fix anatomy by trimming conjunctiva in case of conjunctivochalasis; remove pterygiums and fix eyelid issues like ectropion and entropion; tell patients to use over-the-counter artificial tears first and refer if persistent symptoms; change environmental conditions if happens with prolonged screen time (take breaks, use artificial tears periodically while at computer), add humidifier; refer if ineffective

Cataract: anterior chamber disorder; leading cause of blindness worldwide; cataract is a change in the lens; refractive surfaces of the eye are cornea (provides 40 diopters refractive power) and lens (provides 20 diopters refractive power), which work together to get light to retina to see clear image; lens is metabolically active and changes over time; when young, lens is blue and easy to see through; with age, color changes to yellowish-green-brown color and becomes more opalescent (less able to shine light through it); development of cataract does not necessitate surgery; anyone over age 50 has some sort of lens change; look for lens opacity that is visually significant; happens at different time for different people; a person may have minor lens change, but if they are a photographer, they really notice it; some have vision of 20/70 and they can no longer watch TV; let patient tell when vision significantly affected; rare traumatic emergencies with penetration of capsule requires urgent cataract removal; cataract surgery usually elective

Retinal Disorders

Macular degeneration: retinal disorder with genetic and environmental components; whites more commonly affected than blacks, who, if affected, tend to have variant form; macula is center part of retina that supplies central vision; look for changes like drusen (yellow deposits) and atrophy of choroid (layer under retina that supplies retina with nutrients); two forms; wet form has abnormal vessels growing into retina; dry form has no abnormal vessels; optical coherence tomography (OCT) provides cross-sectional view of retina and shows vessels as fluid spaces within and under retina; important to distinguish between forms because wet macular degeneration treated with periodic anti-vascular endothelial growth factor (VEGF) injections, whereas dry macular degeneration with moderate or severe drusen (size, how fluffy, how much atrophy) treated with AREDS (age-related eye disease studies) vitamin formulation (vitamin C and zinc); vitamins modestly reduce risk of progression to wet macular degeneration; patients' vision should be monitored for conversion from dry to wet; better visual prognosis if anti-VEGF therapy started soon after conversion

Retinal detachment: three types; rhegmatogenous retinal detachment results from tear; exudative retinal detachment results from fluid underneath retina; traction-related detachment; most common form results from tear with vitreous fluid tracking underneath retina causing detachment; biggest risk factor is aging, which makes vitreous more liquid and pulls off retina at some points; called posterior vitreal detachment; causes sudden black dot floating in vision that represents condensed part of vitreous floating through more liquefied layers because no longer attached to retina; look for presence of retinal tears, which occur within 4 to 6 weeks of vitreous detachment due to persistent vitreous adhesions to retina that tear with movement; re-check within 4 to 6 weeks; risk for new tear decreases after that; a tear without much subretinal fluid can be treated with laser in clinic to tack down and prevent progression to retinal detachment; if tear missed and enough fluid goes underneath, need surgery; can wrap scleral buckle outside eye to compress area of tear and use cryotherapy, which was preferred approach; now more popular approach is repair of retina from inside using vitrectomy; in complex cases, use both; new onset floaters or flashes of light could indicate a retinal tear and require ophthalmologic evaluation

Retinal vein occlusion: acute vision loss; occurs in older patients with vascular risk (diabetes, hyperlipidemia, hypertension, smoking, metabolic syndromes) and those with raised intraocular pressure; sometimes associated with malignancy, hypercoagulable state; determine what systemic conditions contributing and reduce risk

Central retinal vein occlusion: dramatic presentation of disc swelling, tortuous veins, and heme throughout retina; if ischemic, patients at higher risk developing neovascularization of iris, which closes angle and causes neovascular glaucoma; very challenging to manage, so use laser on ischemic retinal area to decrease overall metabolic load and prevent vessel formation; another strategy is anti-VEGF injections if vessels form

Hemi-vein occlusion (HRVO) or branch retinal vein occlusion (BRVO): similar presentation of tortuous veins and heme in affected quadrant; much less likely to have neovascularization because less ischemia; main complication is macular edema (fluid accumulation in macula), which decreases vision; treat with anti-VEGF injections every 1 to 3 months; OCT very useful to screen for macular edema, but clinical exam crucial to evaluate for presence of iris neovascularization

Retinal artery occlusion: less common but similar risk factors to central retinal vein occlusion; embolic disease affects central retinal artery or branch; visual loss is more devastating in central retinal artery occlusion than central retinal vein occlusion; very small arteries with diffuse

retinal whitening and cherry red spot; fovea appears red because contrasts with retinal swelling in surrounding retina; attempts to restore vision with eye massage to dislodge emboli or lower pressure, but nothing changes course or visual prognosis, which is guarded; main goal to treat systemic disease like diabetes, hyperlipidemia; consider giant cell arteritis or temporal arteritis as underlying etiologies

Endophthalmitis: infection within eye; exogenous endophthalmitis associated with recent eye surgery and pathogen introduced through surgical wound; endogenous endophthalmitis associated with systemic infection and need to find source; sample fluid from front part of eye or vitreous cavity; inject antibiotics into eye before waiting for confirmatory culture because faster control is better; after culture results, treat locally with intracameral or intravitreal antibiotics or antifungals; if severe, surgical cleaning of vitreous cavity to decrease burden of infectious organisms; prognosis guarded and depends on type of organism; *Staphylococcus epidermidis* after cataract surgery has better prognosis than *Streptococcus* species

Cellulitis: orbital cellulitis versus periorbital cellulitis; periorbital does not involve orbital septum and has much better prognosis; orbital cellulitis can affect optic nerve and cause visual loss; differentiate clinically and with imaging; patient with orbital cellulitis should be hospitalized and treated with intravenous antibiotics; periorbital cellulitis observed, treated with oral antibiotics; signs of orbital involvement include vision loss, optic nerve involvement (afferent pupillary defect), restriction of eye movement, proptosis; treat, monitor orbital more closely

Optic neuritis: inflammation of optic nerve; presentation is decreased vision with color vision loss, pain with eye movement; can be associated with multiple sclerosis (MS)

Anterior ischemic optic neuropathy (AION): acute vision loss; optic nerve slightly swollen; determine if associated with temporal arteritis, which makes vision loss worse; optic nerve is pale, chalky white; non-temporal arteritis-associated AION associated with diabetes, hypertension; vision loss may not be as severe and optic nerve does not look as bad; sectorially but not diffusely swollen, not chalky white; differentiate between arteritic process (associated with temporal arteritis) or non-arteritic process; look at optic nerve, determine if optic neuropathy and subtype

Trauma: should cause concern about globe, as in superficial lesions of corneal abrasion or conjunctival laceration (heal without intervention); fluorescein strip to see if epithelial disruption on ocular surface; worry about penetration of object into eye or laceration; trauma patients may have multiple issues and eye exam often delayed; look at eyeball, gently check if pressure low, which is a sign of laceration or penetration; see if anterior chamber is deep, iris is regular, pupil is regular; pupil irregularity with pulling to an area is a sign of penetration; look at white part of eye for bleeding associated with a hole in the eye; type of trauma increases or decreases risk; metal projectiles easily penetrate eye; small penetrations may be missed; if anterior segment looks funny, put shield over eye, do not let patient rub eye; low threshold for referral, especially if person was working with metal or says there was a high-impact foreign body that went toward the eye; if patient reports that a leaf or dirt fell into eye, penetration less likely; injuries involving plants (branch, thorn) may cause infections with fungi or bacteria; treat with antibiotics and follow closely

Uveitis: inflammation of uvea or any part of eye; anterior chamber uveitis/iritis includes scleritis; uveitis categorized by anatomical components that are inflamed; HLA-B27 disorders most commonly associated with iritis; 50% of patients with iritis have systemic association (40% are HLA-B27, sarcoidosis, syphilis)

Intermediate uveitis or vitreitis: inflammation mainly in vitreous cavity; differential includes infections (syphilis, TB, Lyme), inflammatory (MS, sarcoidosis), lymphoma, primary CNS lymphoma

Retinitis: inflammation of retina; typically infection with virus; CMV associated with immunosuppression in HIV; HSV and zoster very serious because retinitis can spread very quickly and cause vision loss; aggressively treat; Behcet's disease less common cause of inflammatory retinitis; focal chorioretinitis is classic presentation of toxoplasmosis, associated dense vitreitis over lesion; treatment of infection plus oral corticosteroids 48 hours after starting anti-infective (double strength Bactrim twice a day to deal with inflammatory consequences of toxoplasmosis); choroiditis seen in multiple conditions (most commonly sarcoidosis); diseases of retina and choroid without systemic diagnosis such as multifocal choroiditis with panuveitis, in which the anterior chamber vitreous is inflamed and there are punched up choroidal lesions; determine if disease localized or systemic; treat inflammatory anterior uveitis with topical corticosteroids but may need local injections or systemic therapy if there is need to penetrate to vitreous or posterior part of eye or if systemic

Suggested Reading

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Allergic and Immunologic Disorders

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Overview

Background: allergies among most common chronic conditions worldwide; most allergic reactions mediated by allergenic proteins binding to specific IgE antibodies, leading to crosslinking of receptors on mast cells and basophils, triggering release of vasoactive mediators including histamine and tryptase; symptoms can occur in any organ system; allergic reactions can range from mild (*eg*, hives) to severe life-threatening reactions (anaphylaxis); many allergens responsible for allergic reactions; most common include environmental allergens (eg, pollens, dust mites), insect stings, medications, foods

Allergic Rhinitis

Overview: symptoms often occur in spring and fall; 10% to 30% of general population; IgE-mediated inflammation of nasal-ocular area; repeated exposure to aeroallergens can lead to allergic sensitization in susceptible individuals; subsequent exposure to allergens in sensitized patients can trigger IgE-mediated symptoms; symptoms can be seasonal, triggered by tree, grass, weed, ragweed pollens; some patients have perennial symptoms due to indoor allergens (*eg*, dust mites, cockroaches, mice, mold, cat or dog dander); nasal symptoms include pruritus, sneezing, rhinorrhea, congestion; postnasal drip can trigger cough; severe rhinitis symptoms can lead to loss of taste and smell, as well as sleep disturbance; concomitant allergic conjunctivitis can occur, with ocular itching, sneezing, and/or tearing; *physical findings* — Dennie-Morgan lines (folds below lower eyelids); allergic shiners (infraorbital edema and darkening); transverse nasal crease (from repeated upward rubbing of the nose); enlarged, pale nasal turbinates; clear nasal discharge; "cobblestoning" of posterior pharynx; eyes may show bilateral redness and chemosis or conjunctival edema

Diagnosis: often made clinically; allergen-specific testing, either serum testing for allergen-specific IgE or skin-prick testing, to identify allergic sensitization

Differential diagnosis for nasal symptoms: *upper respiratory tract infection (URTI)* — duration of symptoms generally shorter; nasal and ocular itching less prominent; *chronic nonallergic rhinitis* — generally causes perennial symptoms (however, these patients test negative for aeroallergens); patients can report exacerbations of symptoms with changes in temperature, humidity, or alcohol; *rhinitis medicamentosa* — history of vasoconstrictor or decongestant nasal spray use; patients often have swollen, red nasal mucosa; *atrophic rhinitis* — can be seen in elderly patients with complaints of chronic congestion, halitosis, and crusting of nose; patients have thin, erythematous nasal mucosa and test negative for aeroallergens; *nasal polyps* — severe nasal congestion or obstruction, anosmia common

Differential diagnosis for ocular symptoms: *viral conjunctivitis* — often acute, unilateral, associated with antecedent URTI; *bacterial conjunctivitis* — redness in one or both eyes; mucopurulent discharge

Management: pharmacotherapy for symptom control; allergen avoidance; *pharmacotherapy* — include intranasal glucocorticoids; oral, intranasal and/or ocular antihistamines; oral leukotriene inhibitors; intranasal cromolyn; intranasal glucocorticoid monotherapy initial first-line treatment for seasonal allergic rhinitis; nasal saline irrigation can also be beneficial; *allergen avoidance with environmental control measures* — to decrease allergen exposure; can include dust mite — impermeable encasements for pillows and mattresses, pet removal, control of pest infestation, avoiding high humidity in home (which can promote dust mite and mold growth); pollen avoidance includes closing car and home windows and staying indoors during high pollen times; *allergen immunotherapy* — only disease-modifying treatment available; involves administration of gradually increasing doses of allergen extracts to induce long-lasting tolerance to allergens; subcutaneous administration used clinically for >100 yrs; typical course of treatment lasts 3 to 5 yrs; prolonged benefits often seen several years after discontinuation; side effects include local and systemic reactions, including anaphylaxis; frequency of systemic reactions <1%; *sublingual immunotherapy* — products for grass, ragweed, and dust mites recently FDA approved; self-administration, lower risk of anaphylaxis; referral to specialist indicated for severe symptoms or if refractory to therapy

Insect Stings

Background: stinging insect allergy IgE-mediated reaction to proteins in insect venoms; *Hymenoptera insects* — *eg*, wasps, yellow jackets, hornets, bees, fire ants; responsible for majority of serious sting-related reactions; reactions can be characterized as local, large local, or systemic

Presentation: can include sudden onset of diffuse hives and difficulty breathing after first-time sting; *local reaction* — typical local reaction red, painful swelling at site of sting that develops within minutes and resolves within few hrs; not considered allergy; *large local reactions* — occur in 10% to 15% of adults; localized

swelling developing over 1 to 2 days, contiguous to sting site; swelling subsides in 5 to 10 days; patients have low risk for systemic reactions to future stings; *systemic cutaneous reactions* — generalized skin symptoms; urticaria, angioedema, and/or erythema not contiguous with sting site; patients also have low risk for anaphylaxis with subsequent stings (~<3% within 10 to 20 yrs); *most severe reactions* — systemic reactions not isolated to the skin; includes potentially life-threatening anaphylaxis; affects ~3% of adults; patients with mastocytosis have higher frequency of systemic reactions to insect stings; for these patients, insect stings most common cause of anaphylaxis, and anaphylactic reactions more likely severe; *systemic reaction symptoms* — can affect (as noted above) — can include urticaria, flushing, angioedema; can also affect other organ systems; *respiratory symptoms* — hoarse voice or upper airway obstruction due to pharyngeal edema, shortness of breath, wheezing from bronchoconstriction; *cardiovascular symptoms* — range from lightheadedness to hypotension, shock, and circulatory collapse indicate severe sting anaphylaxis; majority of fatal reactions result from circulatory collapse; in adults, absence of skin symptoms associated with more severe reactions

Diagnosis: generally reserved for situations in which venom immunotherapy is or may be indicated; patients with history of anaphylaxis to insect sting should have allergen-specific testing to confirm sensitization or presence of specific IgE to insect venoms, and to determine which venom should be used in immunotherapy; skin testing preferred to serum IgE testing because more sensitive and less expensive; test at least 4 to 6 weeks after sting, because many patients demonstrate reduced skin sensitivity to venom allergens within first few wks after systemic reaction

Nonallergic reactions to insect stings: toxic reactions can occur if numerous stings occur simultaneously; Hymenoptera venoms have vasoactive properties that can cause symptoms including nausea, vomiting, diarrhea, headache, vertigo, syncope, convulsions, fever; hemolysis, cardiac complications, renal failure, rhabdomyolysis have also been described in cases of severe toxic reactions; uncommon; other types of systemic reactions include serum sickness, vasculitis, myocarditis, encephalitis

Management: patients with systemic reactions should be prescribed self-injectable epinephrine and instructed on proper use; subcutaneous immunotherapy for insect sting allergy uses same principles as for aeroallergens; venom immunotherapy can reduce risk of recurrent life-threatening reaction to subsequent stings from 30% to 60% to <5%; patients with possible systemic reaction should be referred to allergy specialist for evaluation, diagnosis, and treatment; in those with systemic reactions that include organ systems other than skin, venom immunotherapy indicated; those with family history of insect sting allergy do not require allergy testing because asymptomatic sensitization to venoms may be as high as 40%; risk of experiencing systemic reaction to insect sting ~3% (same as the general population)

Drug Allergy

Background: adverse reaction caused by immunologic response elicited by drug; immediate reactions IgE mediated and carry risk of potential life-threatening anaphylaxis if drug readministered; signs and symptoms of allergy commonly appear within minutes after exposure, but may begin after 1 to 2 hrs following oral administration; *commonly implicated drugs* — beta-lactam antibiotics, neuromuscular blocking agents, quinolones, platinum-containing chemotherapeutic agents, foreign proteins, including chimeric antibodies (*eg*, cetuximab, rituximab); penicillin allergy most common drug allergy reported (≤10% of patients); however, >90% of patients with reported penicillin allergy do not have IgE antibodies seen on skin testing, because either they were inappropriately labeled as allergic or allergy resolved; studies suggest that, among patients with an IgE-mediated penicillin allergy confirmed with skin testing, 97% tolerate cephalosporins and 99% tolerate carbapenems

Diagnosis: penicillins among leading causes of drug-induced anaphylaxis; identify suspect drug by evaluating clinical history of recent and past drug reactions, reviewing dose and route of administration, and determining temporal associations between administration of drug and development of symptoms; penicillin skin testing reagents commercially available and skin testing well validated; if positive, allergy confirmed, and patient should avoid penicillins or undergo desensitization if needed; if negative, graded challenge should be performed, which includes administering drug in graduated manner under close observation; if no reaction during challenge, highly unlikely, though not impossible, drug will cause allergic symptoms in future; for most other drugs, full range of metabolites and intermediate forms of the drug to which patient may become allergic not defined and testing reagents not available; only native (unmetabolized) form of drug can be used for testing, but may only detect fraction of allergic patients; positive test supports allergy; negative test result does not exclude allergy because patient may be allergic to metabolite or intermediate form; in vitro tests for immediate drug reactions commercially available, but predictive values not well defined

Management: 3 main options; administration of unrelated, but comparable medication; careful administration of related medication; or desensitization to culprit drug; if patient requires treatment with culprit drug, desensitization may be appropriate; drug desensitization temporarily induces short-term tolerance, allowing safe administration of uninterrupted course of medication; desensitization renders mast cells unresponsive to drug; effective as long as patient continues to receive drug; sensitivity returns after discontinuation, so patient needs to know desensitization process temporary and allergy still present; referral to allergist for evaluation and definitive diagnosis encouraged for patients with possible drug allergy who may need drug/related drugs

Nonallergic drug reactions

Serum sickness reaction: common history includes fever, purpuric rash, arthralgias 2 wks after starting drug, with symptom resolution 4 wks after discontinuation; immune complex–mediated hypersensitivity, not IgE-mediated allergy; skin testing in serum-specific IgE testing only informative for IgE-mediated allergies; culprit drug

should be avoided because re-exposure may lead to more rapid and more severe serum sickness reaction

Other delayed drug reactions: also not IgE-mediated, so allergy testing not useful; can be life threatening; *drug-induced hypersensitivity syndrome (DRESS)* — drug reaction with eosinophilia and systemic symptoms; fever, skin symptoms, facial edema, lymphadenopathy, internal organ involvement, and hematologic abnormalities (*eg*, eosinophilia, lymphocytosis, thrombocytopenia); antiepileptic agents and allopurinol most common causes; DRESS has long latency, onset usually 2 to 6 weeks after starting drug; *Stevens-Johnson syndrome and toxic epidermal necrolysis* — severe blistering skin disorders, potentially life-threatening reactions; fever and mucocutaneous lesions leading to necrosis and sloughing of epidermis

Food Allergy

Background: can cause diffuse pruritus, hives, nausea, and vomiting after ingesting peanuts; adverse food reactions can be immunologically mediated or nonimmunologic; food allergy mediated by allergen-specific IgE antibodies; upon exposure, symptoms develop within minutes to 2 hrs; reactions can range from mild symptoms to severe life-threatening reactions or anaphylaxis; can affect any organ system, including the skin, gastrointestinal (GI), respiratory, and/or cardiovascular systems; affects 2% to 5% of adults; most common allergens are peanuts, tree nuts, fish, shellfish; many present in childhood, but some may be diagnosed in adulthood

Diagnosis: detailed history; skin and/or serum testing for specific IgE to provide supporting evidence of sensitization; indiscriminate testing for many different foods not advised because sensitization, or detectable IgE alone, not sufficient for diagnosis; many are sensitized to foods but without clinical symptoms

Differential diagnosis: nonallergic adverse reactions to foods; examples include gastroesophageal reflux, GI infection, and lactose intolerance due to deficiency of lactase enzyme; strawberries and berries naturally contain histamine-like or histamine-releasing compounds that may trigger mild skin symptoms of contact urticaria; other foods can cause local irritation of mouth (*eg*, pineapples)

Management: allergen avoidance and preparation with self-injectable epinephrine in case of allergic reaction; instruct to read ingredient labels on packaged foods and how to prepare safe meals; provide strategies for navigating restaurants and other food-serving venues; patients with suspected IgE-mediated food allergy should be referred to allergy specialist for definitive diagnosis and further management; several potential therapies currently under investigation to minimize risk for accidental exposures and allergic reactions

Oral allergy syndrome: IgE-mediated contact allergy, affects 30% to 70% of people with pollen allergies; caused by homologous proteins in pollens and fresh fruits and vegetables such as apples; relevant proteins sensitive to heat, acid, digestion; symptoms often limited to oropharynx; cooked forms well tolerated; <10% experience systemic reactions

Common Variable Immunodeficiency (CVID)

Background: primary immunodeficiency; most prevalent form of severe antibody deficiency affecting adults; characterized by impaired B-cell differentiation, with defective immunoglobulin production; presents with heterogeneous clinical manifestations such as recurrent infections affecting different organ systems, chronic lung disease, autoimmune disorders, GI disease, heightened susceptibility to lymphoma; estimated to affect ~1 in 25,000 individuals; although manifestations can begin in childhood, most patients diagnosed at age 20 to 40 yrs; results from many genetic defects, but, thus far, specific defects have only been identified in small subset

Diagnosis: measure quantitative immunoglobulins; IgG decreased, generally <400 mg/dL; IgA and/or IgM also decreased; levels should be repeated to confirm persistently low values; vaccine responsiveness should be assessed; usually impaired responses to both protein- and polysaccharide-based vaccines

Differential diagnosis: secondary hypogammaglobulinemia due to either decreased production or increased loss; decreased immunoglobulin production can be caused by drugs (*eg*, immunosuppressants, rituximab, antiepileptics), malignancy, or Good syndrome (thymoma with hypogammaglobulinemia); increased loss can be seen in protein-losing enteropathy, nephrotic syndrome, or fluid loss from trauma

Management: immunoglobulin replacement mainstay of treatment; administered intravenously or subcutaneously; treatment reduces number of infections and decreases antibiotic use and hospitalization; although immunoglobulin replacement slows progression of chronic lung disease, GI infections, and/or complications relatively unaffected; antibiotics for treatment of acute infections or exacerbations of chronic infections, as well as prophylactically; certain live vaccines should not be given, particularly for CVID patients with significantly impaired T-cell function; monitor for complications; major causes of death complications from chronic lung disease and malignancies; referral to clinical immunologist indicated to exclude other causes of hypogammaglobulinemia, determine most appropriate therapies, and monitor for associated disorders

Selective IgA Deficiency

Background: most common immune defect; isolated deficiency of serum IgA; rule out other causes of hypogammaglobulinemia; clinical manifestations vary, can include recurrent infections and autoimmune disease; most individuals asymptomatic; most significant risk factor family history of either IgA deficiency or CVID; less than one-third require medical attention; patients usually present with recurrent sinopulmonary infections, autoimmune disorders, *Giardia* infections or other intestinal disorders, allergic disease, anaphylactic transfusion reactions (rare); low serum IgA and normal IgG and IgM levels

Management: asymptomatic patients do not require treatment beyond education and periodic follow-up; for symptomatic patients, treatment of specific infection or allergic or or autoimmune disorder; prophylactic antibiotics may be indicated for those with continued infections despite management of predisposing

conditions (*eg*, allergic rhinitis, asthma, chronic rhinosinusitis); immunoglobulin replacement therapy occasionally indicated if prophylactic antibiotics fail to reduce number of infections; generally, few patients with IgA deficiency require immunoglobulin to control infections; patients with severe IgA deficiency (levels <7 mg/dL) and those with partial IgA deficiency who have experienced transfusion reactions should be screened for anti-IgA antibodies to assess risk for future infusion reactions to blood products; patients who test positive for anti-IgA antibodies require special precautions if future blood products required; referral to specialist recommended

Key Points

1. IgE-mediated allergies can occur to environmental allergens, insect stings, medications, and foods. Symptoms can range from mild to severe, so patients should be educated on allergen avoidance to minimize the risk of reactions. Patients with insect sting or food allergy should be prepared with self-injectable epinephrine in case of accidental allergen exposure leading to severe reactions.
2. Immunotherapy is a treatment option for allergic rhinitis and insect sting allergy. Treatment can lead to a reduction in allergic rhinitis symptoms or reduction in risk of recurrent life-threatening reaction to subsequent insect sting in those with history of systemic reactions not isolated to skin.
3. Up to 10% of patients report penicillin allergy, but >90% do not have IgE antibodies when tested. Therefore, evaluation important.
4. Selective IgA deficiency most common immunologic defect. Most affected individuals asymptomatic and less than one-third have clinical manifestations, which can include recurrent infections and autoimmune disease.

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Psoriasis

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Psoriasis

Background: affects 2% of population; about 150,000 to 200,000 new cases each year; all races, although whites more often affected than blacks; generally bimodal age of onset (0s and 50s), although can develop at any point; physical, psychological, and social impact; *important to keep psychosocial impact in mind* — can be very debilitating; patients with psoriasis have higher incidence of depression; about 30% develop psoriatic arthritis, which can be disabling; etiology includes genetic associations — ie, familial; disorder of dysregulated inflammation; alterations at cellular levels; alteration in keratinocyte kinetics — shortened cell cycle, marked increase in production of epidermal cells; type 1 T helper cell (Th1) response is robust; milieu of cytokines in circulation that can lead to systemic complications;

Diagnosis: classic form has several characteristics, but uncommon forms exist; *differential diagnoses* — fungal infections, seborrheic dermatitis, drug rashes, cutaneous T-cell lymphoma, *etc*; *common areas of involvement* — scalp, elbows, knees, back, umbilical area, gluteal clefts; sometimes face, palms, soles, nails; should examine scalp and nails if patient presents with diffuse rash; generally, biopsy not required, but with some variants, can be helpful to confirm diagnosis; *classic rash of psoriasis* — red, scaly plaque with sharp borders, well demarcated from surrounding skin; scales may be covered with scale, which may be silvery or whitish; in all types of psoriasis, nail involvement has classic findings; pitting, onycholysis, both nonpathognomonic (can also be seen with subungual hyperkeratosis) and pathognomonic "salmon patch," pink patch under nail bed, caused only by psoriasis

Uncommon forms: *inverse psoriasis* — usually in intertriginous areas, *eg*, axilla, groin, under breasts; patches (thinner than classic plaques); no scale; found in atypical areas; frequently misdiagnosed as candidal infections (*eg*, if treating with antifungal/dermatophyte agents and no improvement, consider inverse psoriasis and prescribe low-potency topical corticosteroid instead); *uncommon types* — palmar-plantar psoriasis; guttate psoriasis, demonstrated by hundreds to thousands of papules with scale, often occurring after streptococcal infection; sometimes treating streptococcal infection can improve guttate psoriasis; if not, referral to dermatologist for light therapy or systemic; pustular variants such as von Zumbusch psoriasis, severe form that can include fever, arthralgias, and pustular lesions (can have 5% mortality rate); erythrodermic psoriasis, in which skin turns red and sloughs off throughout body, but broad differential diagnosis; severe forms may need biopsy for definitive diagnosis; pustular and erythrodermic variants sometimes *medication related* — systemic steroid withdrawal can cause flare of either pustular or erythrodermic psoriasis; important to note when giving steroids for nonskin conditions, *eg*, decompensated asthma

Comorbidities: inflammatory skin disease, has complex etiology involving genetic and environmental factors; relationship between psoriasis and other diseases has drawn increasing interest recently; evidence now suggests that cardiovascular disease, obesity, diabetes, hypertension, dyslipidemia, metabolic syndrome, nonalcoholic fatty liver disease, cancer, anxiety and depression, and inflammatory bowel disease found at higher rate in patients with psoriasis; unsure whether due to shared risk factors (*eg*, smoking, alcohol consumption, treatment); early detection and treatment of comorbid conditions associated with psoriasis important; need integrated approach to ensure treatment of psoriasis does not interfere with the management of comorbid conditions, and vice versa

Severity grading and treatment: mild psoriasis involves <5% body surface area; moderate to severe psoriasis 5%-10% body surface area; severe psoriasis >10% body surface area; each individual patient should be treated based on psychosocial as well as physical concerns; some patients with mild disease medically can perceive condition as severe, and vice versa

Psoriatic arthritis: certain patterns of joint involvement; asymmetrical arthritis of distal interphalangeal joints; seronegative spondyloarthropathy, which can resemble rheumatoid arthritis; bilaterally symmetrical; "sausage digits"; consider anti-tumor necrosis factor (TNF) agents and/or methotrexate; generally requires referral to either rheumatologist or dermatologist

Treatment options: for severe disease, can refer to dermatologist for ultraviolet light, either as ultraviolet B (UVB) or psoralen (photosensitizing agent) and ultraviolet A (PUVA); also can consider either systemic or biologic agents; if limited or mild disease, reasonable for nondermatologists to employ topical therapies; for moderate to severe disease, can use topical, systemic, and/or ultraviolet therapy

Topical corticosteroid therapy: numerous options; rational administration of topical corticosteroids important; not benign medications; mainstay of treatment, not only for psoriasis, but for many other dermatoses; many generic low-cost options; come in multiple potencies and delivery vehicles; can be used with light therapies or with some systemic medications; low-potency, mid-potency, and potent topical corticosteroids; *low-potency corticosteroids*

*(*eg*, generic hydrocortisone)* — for areas of the body where skin is thinnest, around the eyes and other parts of the face, in the intertriginous areas, on the genitalia, around the anus, and for chronic dermatosis; *mid-potency corticosteroids (*eg*, triamcinolone 0.1%; triamcinolone 0.1% more potent than either hydrocortisone 1% or 2.5%; generic and inexpensive)* — for areas with thicker skin (*eg*, trunk and extremities; *potent corticosteroids (*eg*, halogenated steroids such as halobetasol, clobetasol, betamethasone)* — for areas with thickest skin, such as palms or soles; for patient with severe dermatosis or in need of quick improvement, can increase from low-potency to mid-potency or mid-potency to potent for maximum of 2 wks; important to understand quantities of medications and to recognize amount of medication available in tubes by gram to avoid over- or underprescribing; *potential local side effects of topical corticosteroids* — hypopigmentation, atrophy, purpura, striae; *potential systemic side effects* — suppression of the hypothalamic-pituitary-adrenal axis, Cushing diseases, glaucoma, diabetes mellitus, and hypertension; remember rebound effect when withdrawing topical corticosteroids

Other topical agents: calcipotriene (vitamin D analog) common secondary topical agent; other agents include topical retinoids (*eg*, tazarotene), anthralin, tars; important not to underemphasize importance of emollients and, sometimes, keratolytics; scale must be broken down for some medications to penetrate plaque; calcipotriene takes ≤2 to 3 wks to become effective; slower onset than topical corticosteroids, but can be used in conjugation with them; no association with tachyphylaxis or atrophy; theoretic concern if using >100 grams/wk, can develop hypercalcemia; tazarotene irritating to normal skin; can use for scalp, face, and inverse psoriasis; can use with topical corticosteroids; avoid use during pregnancy because retinoid; anthralins cause staining and irritation; start at very low concentrations (ie, 0.05%-0.1%) and gradually increase to 3% to 5%; coal tar, or liquor carbonis detergens (LCD), can be malodorous, skin staining; newer preparations more cosmetically acceptable

Scalp psoriasis: very common; several topical agents; selenium sulfide (*eg*, SelRx Shampoo, Selsun Blue Shampoo, Tersi Foam); zinc pyrithione (*eg*, Free and Clear Medicated Anti-Dandruff Shampoo, Head and Shoulders, Vanicream Z-Bar); tars (*eg*, DHS Tar Shampoo, Psoriatrix Coal Tar Shampoo, T/Gel Shampoo); corticosteroid lotions; salicylic acid preparations; vitamin D analogs

Drug Eruptions

Background: variable presentations of drug eruptions; common; need to avoid areas of over- and underconcern; range from mild to life threatening; about 2% to 3% of hospitalized patients have some form of cutaneous drug reaction; about 5% of patients can have drug eruption with certain antibiotics; *some patients more prone to these reactions* — *eg*, human immunodeficiency virus (HIV)– positive patients have higher incidence of drug eruptions with trimethoprim-sulfa than those without HIV also higher incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN); when taking history, important to ask not only about prescribed medications, but also over-the-counter medications, herbals, illicit drugs; certain human leukocyte antigen (HLA) genotype populations predisposed to cutaneous drug eruptions; HLA-B 1502 with carbamazepine and Stevens-Johnson syndrome; HLA-B 5701 with abacavir hypersensitivity; HLA-B 5801 and allopurinol, Stevens-Johnson syndrome, etc; also familial predisposition to sulfonamide and aromatic anticonvulsive reactions; slow acetylators have higher risk of drug-induced lupus erythematosus

Types of drug eruptions: most idiosyncratic; allergic variants can occur, usually with drugs with atomic weight <1000 Da, which occurs with prior exposure to the medication; in general, latency of 1 to 2 wks between initial exposure and onset of rash; however, with rechallenge, can be seen within 1 to 2 d; important to note that not dose dependent; also pseudoallergic type, *ie*, anaphylactoid, in which mast cells are degranulated directly; can be caused by opiates and radiocontrast; important to know cross-reactivity between beta-lactam allergy and cephalosporins; unlikely cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides

Patterns: important to recognize patterns of skin diseases; exanthematous reactions and urticarial drug eruptions most common; *urticaria and angioedema* — usually type 1 hypersensitivity; sometimes related to anaphylaxis; evanescent erythema, edematous, intensely pruritic; individual lesion lasts <24 hours, although process can continue in different areas of body for days; if an individual urticarial lesion lasts >24 hours, consider urticarial vasculitis, because typical urticaria from most causes more evanescent; can have angioedema of the lips, tongue, larynx; virtually any drug can cause urticaria and/or angioedema

Erythema multiforme, Stevens-Johnson syndrome, and TEN: used to be considered spectrum; not necessarily true because erythema multiforme usually infectious in origin; most commonly herpes simplex, but mycoplasma and several other infections as well; typical target-type lesions; Stevens-Johnson syndrome and TEN usually medication related; in Stevens-Johnson syndrome and TEN, fever, painful skin, multiple targetoid lesions that can become necrotic macules that can progress to bullae or sloughing; *mucosal involvement* — eyes, esophagus, genital mucosa, mouth, lips; generally, Stevens-Johnson syndrome <10% body surface area involvement with mucosal involvement; when 10% to 30% body surface area involvement, called Stevens-Johnson syndrome/TEN overlap; TEN generally involves >30% of body surface area; *can also have organ involvement* — sepsis, fluid and electrolyte disturbances; renal, pulmonary, gastrointestinal (GI), and ocular involvement; TEN has high mortality, up to 25% to 50%; treatment for TEN evolving; intravenous immunoglobulins (IVIG) and/or systemic corticosteroids may or may not be beneficial; more recently, some using cyclosporine; early evidence that some biologics (*eg*, etanercept) may be beneficial

Vasculitic drug reaction: small-vessel vasculitis; commonly presents with palpable purpura, most commonly in gravity-dependent areas, usually legs; lesions caused by circulating antibody immune complexes that deposit in vessels and activate complement; other organs may be involved; arthralgias; kidney, GI, central nervous system (CNS), even pulmonary involvement; patients presenting with vasculitis typically have palpable purpura in lower extremities; differentials include infections,

Henoch-Schönlein purpura, collagen vascular diseases paraneoplastic syndromes, and idiopathic variety

Drug hypersensitivity syndrome: uncommon; severe; once known as drug reaction with eosinophilia and systemic symptoms (DRESS) but growing appreciation that not all patients have eosinophilia; many causative medications including seizure medications, sulfonamides, allopurinol, abacavir, minocycline, several others; exanthematous, urticarial, erythrodermic types; commonly fever, pharyngitis, adenopathy; hepatitis, transaminitis, leukocytosis, acute interstitial nephritis, pneumonitis, CNS involvement possible; steroids or IVIG often used for treatment; important to note that, with any severe drug reactions, such as TEN and drug hypersensitivity syndrome, need to identify causative agent and withdraw it as soon as possible

Acute generalized exanthematous pustulosis: less common; patients present with confluent erythema, pinpoint subcorneal pustules; pustules typically start on face and spread downward; may have fever, leukocytosis with neutrophilia; T-cell–mediated disorder; most common causative agents include antibiotics such as macrolides, beta-lactams, and quinolones; treatment includes discontinuing medication, possibly adding steroids

Erythroderma: can be either exfoliative or nonexfoliative; can present *de novo* as erythroderma or can start as dermatitis or morbilliform drug reaction; common causes include gold, pyrazolone derivatives, phenytoin, dapsone, lithium; virtually entire skin has blanchable erythema; desquamation common; oral involvement rare

Exanthematous drug reactions: more common; also referred to as morbilliform drug reaction, maculopapular rash, scarlatiniform rash, toxic erythema, or drug rash; blanchable erythema of macules and papules; severe cases can progress to confluent and/or reticulated erythema; usually start proximally and move distally; usually no significant morbidity; any drug can cause; if causative agent is lifesaving medication, acceptable to continue

Fixed drug reaction: not severe; focally recurrent erythema and edema; lesions tend to be round, may have targetoid appearance with large central dusky zone, and some surrounding annular erythematous rim; purple and brown discoloration; will recur at the site of previous involvement if causative drug reinstated; may also develop new sites; often leave some residual pigment after resolution; causes include tetracyclines, sulfonamides, barbiturates, phenolphthalein-containing laxatives, nonsteroidal anti-inflammatory drugs (NSAIDs)

Dischromias: many medications can lead to discoloration of body; tetracyclines, amiodarone, zidovudine (AZT), antimalarials, some chemotherapeutics, others

Other drug reactions: steroid acne; allergic contact dermatitis to topical therapies (neosporin common); vascular endothelial growth factor (VEGF) inhibitors can form acneiform reactions; medications such as sulfa drugs and oral contraceptives can cause erythema nodosum; medications can cause alopecia and/or nail changes; warfarin skin necrosis; certain medications can worsen psoriasis; cause lichen planus; can be associated with pseudoporphyria; drug-induced pemphigoid; many others

Eczema

Background: also known as dermatitis; inflamed skin; variety of different subtypes; if coin-shaped appearance, nummular eczema; asteatotic eczema, common, often seen in elderly, in lower extremities in winter; contact and irritant dermatitis; atopic dermatitis; *symptoms* — cardinal manifestations of eczema include redness, mild to moderate scale, vesicles; often chronic pruritic inflammatory dermatosis; common in lower extremities of elderly patients, especially in colder months because of decreased ambient humidity and home heater usage, which dries skin; with age, sebaceous glands become less active and produce less sebum (*ie*, lipid) on skin, leading to more drying and more evaporative losses, causing micro- and macrofissuring; recurrences tend to be frequent; differential diagnoses include dermatophytes, contact dermatitis, psoriasis, cutaneous T-cell lymphoma; eczema lesions can develop secondary infections from either staphylococcal or streptococcal infections; *nummular eczema* — not enough lipids in skin; treat by applying lipid to the skin; topical emollients most important treatment; *difference among ointments, creams, and lotions* — depends lipid-to-water ratio in vehicle; ointments have most lipid per volume, creams intermediate, and lotions least (*ie*, higher water-to-lipid ratio); for nummular eczema, recommend using "a lot of lipid," *ie*, ointment; best applied after showering or bathing to lock in moisture; use tepid showers and avoid strong detergent soaps; can sometimes employ topical corticosteroids for secondary inflammation

Dyshidrotic eczema: also known as pompholyx; vesicular eczema of hands and feet; acute or chronic; deep-seated, clear microvesicles on fingers, palms, soles; can also see scaling, fissuring, and lichenification; in contrast to typical asteatotic eczema seen in winter, dyshidrotic seen in warmer months; rule out dermatophytosis or contact dermatitis; treatment with medium- to high-potency topical corticosteroids because of thicker skin on palms and soles; use occlusives, such as gloves at night, to make topical corticosteroids more potent; patients may occasionally require oral corticosteroids or PUVA

Atopic dermatitis: most develop by age 12 yrs; 60% develop by age 1 yr, 90% by age 5 yrs; chronic and usually recurrent; can have exacerbations; patients may have personal or family history of asthma, hay fever, allergic rhinitis, or atopic dermatitis; *most important symptom* — severe pruritus; pruritus can lead to an "itch-scratch-rash" cycle; can lead to lichenification (thickening of the skin) with accentuation of skin markings, and worsening dermatitis; can be worsened by stress, skin dehydration, hormonal factors, secondary infection, and certain clothing (eg, wool); *special clinical features* — involvement of skin folds (*eg*, popliteal or antecubital fossa), tendency to have generalized infections and cutaneous herpes simplex, bilateral cataracts, can have atopic shiners, and Dennie–Morgan lines (infraorbital folds); *treatment* — moisturizers, topical corticosteroids, histamine 1 (H1) blockers, stress management, topical cyclosporine, ultraviolet light

Contact dermatitis: acute, subacute, or chronic inflammation of epidermidis and dermis caused by external agent; pruritus, erythema, vesiculation; important to distinguish allergic from irritant dermatitis (*eg*, not all people react to poison ivy [allergic dermatitis], but everyone would demonstrate symptoms after prolonged contact with bleach [irritant dermatitis]); can be localized or generalized; patients sometimes require referral for allergy patch/skin testing to define underlying cause; treatment primarily to removal of irritating agent;

patients may also require wet dressings, cool compresses, topical corticosteroids if somewhat localized, or oral corticosteroids; recommend 40 to 60 mg of prednisone with no taper for 10 days; common pitfall in management is reducing oral corticosteroids too quickly

Key Points

1. Psoriasis affects a large portion of the population and can be both physically and socially debilitating. Several subtypes exist. Treatments include primarily topical agents (specifically corticosteroids, as well as other topical medications), light therapy, and other types of medications.
2. Drug eruptions have variable presentations. Ensure a thorough history is performed to aid diagnosis. Discontinue causative medications where possible.
3. Eczema can present in many forms. The addition of lipid and moisture to the affected skin is key to treatment.

Suggested Reading

Li LF: Bathing and generalized asteatotic eczema: a case-control study. *Br J Dermatol*. 2008;159(1):243-45; **Mustafa SS:** Severe cutaneous adverse drug reactions: presentation, risk factors, and management. *Curr Allergy Asthma Rep*. 2018;18(4):26; **Oji V:** The skin in psoriasis: assessment and challenges. *Clin Exp Rheumatol*. 2015;33(5 suppl 93):S14-9; **Wallach D:** Atopic dermatitis/atopic eczema. *Chem Immunol Allergy*. 2014;100:81-96.