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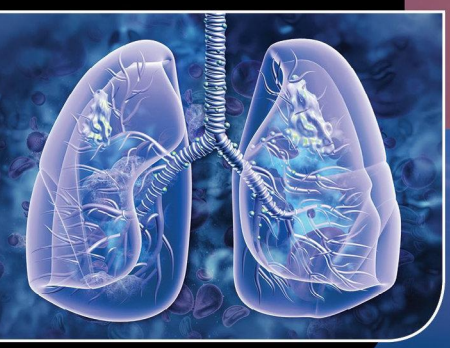

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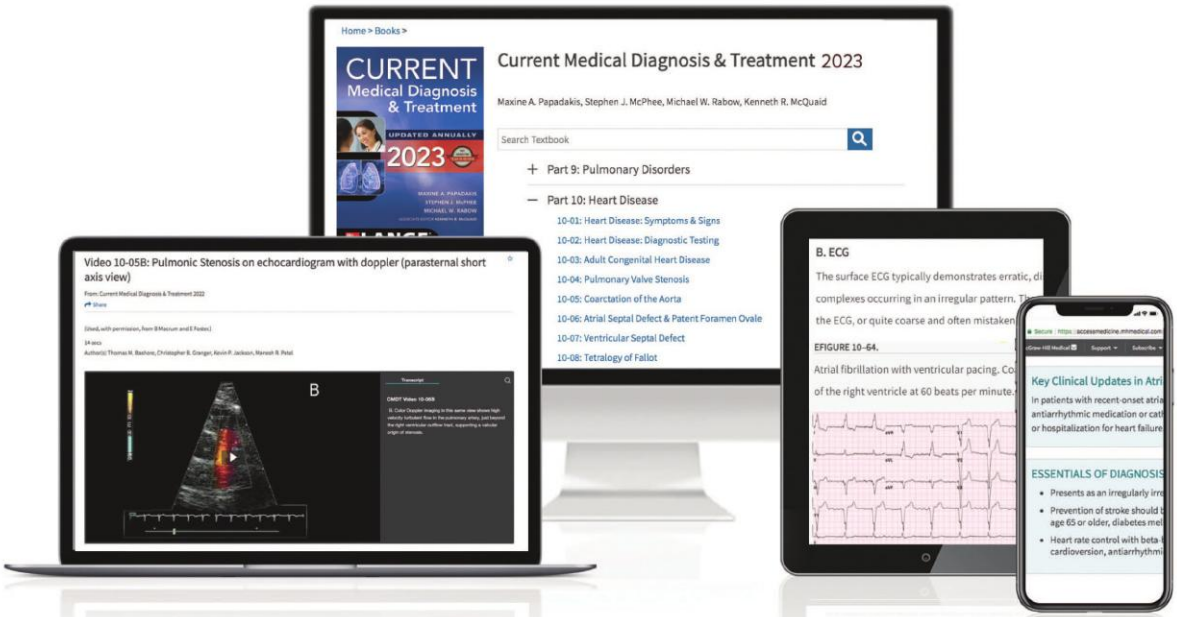

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Preface

Current Medical Diagnosis & Treatment 2023 (CMDT 2023) is the 62nd edition of this single-source reference for practitioners of adult medicine in both hospital and ambulatory settings. The book emphasizes the practical features of clinical diagnosis and patient management in all fields of internal medicine and in specialties of interest to primary care practitioners and to subspecialists who provide general care.

With a growing recognition of systemic racism and other biases in institutions across our societies, including the institution of medicine (https://www.mdcalc.com/race), the editors of *CMDT,* with humility, have committed to a thorough examination of our content to remove biased language, research, and recommendations. Since 2020, we have been pursuing an ongoing, formal process of review and revision in an effort to recognize and correct biases and to promote equity in our book and the practice of medicine. While we, the editors, take this on as our responsibility, we also invite readers to share with us any *CMDT* content that they find problematic or biased.

We have tried to describe populations used in the studies that form the basis of the information in *CMDT,* use appropriate language where we can (eg, persons of sub-Sahara African descent, rather than African-Americans), and use the gender-neutral term Latinx. We acknowledge that, like others,[1] we find this an imperfect solution. We continue, however, to use terms from original sources when study populations are broad.

INTENDED AUDIENCE FOR *CMDT*

House officers, medical students, and all other health professions students will find the descriptions of diagnostic and therapeutic modalities, with citations to the current literature, of everyday usefulness in patient care.

Internists, family physicians, hospitalists, nurse practitioners, physician assistants, and all primary care providers of adult medicine will appreciate *CMDT* as a ready reference and refresher text. Physicians in other specialties, pharmacists, and dentists will find the book a useful basic medical reference text. Nurses, nurse practitioners, and physician assistants will welcome the format and scope of the book as a means of quickly referencing medical diagnosis and treatment modalities.

Patients and their family members who seek information about the nature of specific diseases and their diagnosis and treatment may also find this book to be a valuable resource.

NEW IN THIS EDITION OF *CMDT*

- INNOVATIVE TABLE highlighting the **"Year in Review: Key Clinical Updates in *CMDT 2023*,"** individually listed with page numbers and reference citations, for easy access to significant changes in this edition
- Ongoing concerted effort to address and remove unconscious bias
- List of Common Abbreviations used in *CMDT* can be found on the inside of the front cover
- New section on opioids for pain management
- Overhauled organization of Dermatology chapter to better reflect categorization of conditions and lesions
- Expanded section of interventional therapies to manage chronic pain
- Updated USPSTF lung cancer screening recommendations using low-dose CT
- New prognostic systems for primary myelofibrosis: GIPSS and MIPSSv2
- Discussion of the use of DOACs in patients with morbid obesity who require antithrombotic therapy
- Updated section on osmotic laxatives to treat chronic constipation
- Ozanimod approved for the treatment of moderate to severe ulcerative colitis
- Landmark change in staging female breast carcinoma modifying anatomic stage and adding prognostic stage
- New medications for treating metastatic breast cancer (olaparib, talazoparib, palbociclib, ribociclib, and abemaciclib)
- New recommendations on treating cholestasis of pregnancy
- Updated criteria for diagnosing systemic lupus erythematosus to include antinuclear antibody measurement
- New medications for active lupus nephritis, including voclosporin used with mycophenolate mofetil as well as belimumab
- Anifrolumab is approved for nonrenal lupus when standard therapies fail

[1]April 2021 Annals of Internal Medicine: A Comprehensive Policy Framework to Understand and Address Disparities and Discrimination in Health and Health Care: A Policy Paper From the American College of Physicians. Appendix 2: Glossary.

- New guidelines for diagnosing polyarteritis nodosa
- New American College of Rheumatology/Vasculitis Foundation recommendations for the treatment of granulomatosis with polyangiitis
- A newly described genetic syndrome, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) in the differential diagnosis of relapsing polychondritis
- Discussion of the role of left atrial appendage closure in preventing stroke and systemic embolization
- Aducanumab (anti-amyloid therapy) is approved by the US FDA for the treatment of Alzheimer disease
- Extensive revision of the Thyroiditis section in Endocrine Disorders chapter
- Substantial revision of the Nutritional Support section in the Nutritional Disorders & Obesity chapter
- Substantial revision in the HIV Infection & AIDS chapter, including updates in the available therapeutic regimens
- Rewritten SARS-CoV-2 section and inclusion of SARS-CoV-2 information relevant to specific chapters throughout the textbook
- Extensive revision of Sexual & Gender Minority Health chapter, including sections on family planning and health care for transgender and gender diverse persons

OUTSTANDING FEATURES OF *CMDT*

- Medical advances up to time of annual publication
- Detailed presentation of internal medicine disciplines, plus primary care topics in gynecology, obstetrics, dermatology, ophthalmology, otolaryngology, psychiatry, neurology, toxicology, urology, geriatrics, orthopedics, women's health, sexual and gender minority health, preventive medicine, and palliative care
- Concise format, facilitating efficient use in any practice setting
- More than 1000 diseases and disorders
- Specific disease prevention information
- Easy access to medication dosages, with trade names indexed and current costs updated in each annual edition
- Recent references, with unique identifiers (PubMed, PMID numbers) for rapid downloading of article abstracts and, in some instances, full-text reference articles

E-CHAPTERS, *CMDT ONLINE*, & AVAILABLE APPS

Seven ***e-chapters*** listed in the Table of Contents can be accessed at **www.AccessMedicine.com/CMDT.** These online-only chapters (available without need for subscription) include

- Anti-Infective Chemotherapeutic & Antibiotic Agents
- Diagnostic Testing & Medical Decision Making
- Information Technology in Patient Care
- Integrative Medicine
- Podiatric Disorders
- Women's Health Issues
- Appendix: Therapeutic Drug Monitoring, Laboratory Reference Intervals, & Commonly Used Blood Specimen Collection Tubes

Institutional or individual subscriptions to AccessMedicine also have full electronic access to *CMDT 2023*. Subscribers to ***CMDT Online*** receive full electronic access to *CMDT 2023* as well as

- An expanded, dedicated media gallery; new to this edition are educational videos and printable protocols in the Orthopedic Disorders & Sports Medicine chapter
- ***Quick Medical Diagnosis & Treatment***—a concise, bulleted version of *CMDT 2023*
- ***Guide to Diagnostic Tests***—for quick reference to the selection and interpretation of commonly used diagnostic tests
- ***CURRENT Practice Guidelines in Primary Care***—delivering concise summaries of the most relevant guidelines in primary care
- ***Diagnosaurus***—consisting of 1000+ differential diagnoses

CMDT 2023, QMDT, *Guide to Diagnostic Tests*, and *Diagnosaurus* are also available as individual apps for your smartphone or tablet and can be found in the Apple App Store and Google Play.

SPECIAL RECOGNITION: MITCHELL H. KATZ, MD

With this 2023 edition of *CMDT*, we express our immense gratitude and say goodbye to Mitchell H. Katz, MD as he transitions away from his 30+ years as author of Chapter 31 "HIV Infection & AIDS."

A graduate of Yale College and Harvard Medical School, Dr. Katz completed his residency in the UCSF Primary Care General Internal Medicine Residency, and then trained as a Robert Wood Johnson Clinical Scholar.

Dr. Katz has spent the bulk of his career in public service. He began his work in 1991 in the San Francisco Department of Public Health, ultimately being appointed Director and Health Officer of the Department of Health. He was probably best known for funding San Francisco's successful needle exchange program; for creating its "Healthy San Francisco" Program as the first comprehensive municipal health care and financing system in the United States; for outlawing the sale of tobacco at pharmacies; and for winning ballot measures funding the replacement of the City's 780-bed nursing home, the Laguna Honda Hospital & Rehabilitation Center, and for rebuilding its 386-bed public "safety net" hospital, the Zuckerberg San Francisco General Hospital.

In 2010, Dr. Katz was appointed the Director of the Los Angeles County Department of Health Services (DHS), the second largest public safety net system in the U.S. While in L.A., he created an ambulatory care network that empaneled over 350,000 patients in a primary care home and that transitioned over 4000 medically complex patients from care at hospitals and emergency departments into independent housing, effectively eliminating unnecessary and expensive hospital care and giving these patients the dignity of their own home.

Moving to New York City in 2018, Dr. Katz became President and CEO of NYC Health and Hospitals, the largest municipal health system in the U.S. He is the architect of NYC Care, a health access program that provides comprehensive health care to New Yorkers regardless of income or immigration status. In the spring of 2019, Dr. Katz steered the municipal health system through the worst of the COVID-19 outbreak when NYC was the epicenter of the U.S. pandemic. In a 6-week period, he tripled the number of ICU beds to care for acutely ill patients.

Dr. Katz is an elected member of the National Academy of Sciences and is the Deputy Editor of *JAMA Internal Medicine*. He has published extensively in the areas of HIV epidemiology and health care access. He practices as a primary care physician at Gouverneur Health in Manhattan. Mitch and his partner, Rabbi Igael Gurin-Malous, have two children, Maxwell and Roxie, who were adopted from an orphanage in Vietnam.

As Mitch's editors, we are particularly thankful for his expert annual submissions, providing us a precis about the care of patients with HIV infection/AIDS. We are immensely grateful for his friendship and look forward to hearing about the next chapters in his amazing career of service.

ACKNOWLEDGMENTS

We wish to thank our authors for participating once again in the annual updating of this important book. We are especially grateful to N. Franklin Adkinson, Jr., MD, Antoine Azar, MD, Thomas M. Bashore, MD, C. Seth Landefeld, MD, Manesh R. Patel, MD, George R. Schade, MD, Joshua S. Schindler, MD, and Scott Steiger, MD who are leaving *CMDT* this year. We have all benefited from their clinical wisdom and commitment.

With enormous gratitude and respect, we dedicate this 62nd edition of *Current Medical Diagnosis & Treatment* to all health care professionals and staff who have cared for patients with COVID-19. We honor their competence, their humanity, and their bravery. We also wish to extend our heartfelt gratitude to Eva Clark, MD, PhD, and to Wayne Shandera, MD, for coauthoring (along with Christine Akamine, MD) the authoritative section on COVID-19 (SARS-CoV-2) in the Viral chapter of the print edition of *CMDT* and for providing ongoing, current, and expert updates on this topic in *CMDT Online*.

Many students and physicians have contributed useful suggestions to this and previous editions, and we are grateful. We continue to welcome comments and recommendations for future editions in writing or via electronic mail. The editors' e-mail addresses are below, and author e-mail addresses are included in the Authors section.

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Dedication

Harriet Lebowitz

The editors and publishers of *Current Medical Diagnosis & Treatment* (*CMDT*) wish to dedicate this 62nd edition of *CMDT* to Harriet Lebowitz, in recognition of her more than 20 years of service as our Senior Project Development Editor. Harriet, who is retiring with this edition, has been the major organizing force responsible for the annual production of *CMDT*.

In particular, we would like to express our gratitude to Harriet for her dedication in making *CMDT* the world's number one best-selling annually updated medical textbook in print, online, app, and abbreviated formats (*Quick Medical Diagnosis & Treatment*). Among other innovations that Harriet has contributed, she most recently envisioned and helped create *CMDT's* "Year in Review: Key Clinical Updates" feature.

Throughout many changes over the years, Harriet has been a constant positive presence. Her familiarity with the text, editors, and authors as well as all the arcane details of publishing helped guide our journey to an on-time publication each year. We will all miss working with Harriet very much and wish her the absolute best in her retirement.

YEAR IN REVIEW: KEY CLINICAL UPDATES IN CMDT 2023

Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 2: COMMON SYMPTOMS		
Dyspnea	19	• Point-of-care ultrasonography (POCUS) consistently improved the sensitivities of standard diagnostic pathways to detect heart failure, pneumonia, PE, pleural effusion, or pneumothorax. Specificities increased in most, but not all, studies; in-hospital mortality and length of hospital stay, however, did not differ significantly between patients who did or did not receive POCUS in addition to standard diagnostic tests. *Gartlehner G et al. Ann Intern Med. [PMID: 33900798]*
Dysuria	41	• A systematic review and meta-analysis found D-mannose protective against recurrent UTIs. *Lenger SM et al. Am J Obstet Gynecol. [PMID: 32497610]*
Fatigue & Systemic Intolerance Disease (Chronic Fatigue Syndrome)	34	• Pitolisant, a selective histamine H3-receptor antagonist with wake-promoting effect, may reduce daytime sleepiness in patients with moderate to severe obstructive sleep apnea who do not want continuous positive airway pressure treatment. *Dauvilliers Y et al. Am J Respir Crit Care Med. [PMID: 31917607]*
CHAPTER 4: GERIATRIC DISORDERS		
Dementia	55	• Aducanumab, a monoclonal antibody that targets amyloid-beta protein and promotes its clearance from the brain, became the first new drug approved by the FDA for the treatment of Alzheimer disease since 2003. However, its role in routine clinical care remains unclear. *Lin GA et al. https://icer.org/assessment/alzheimersdisease-2021/*
CHAPTER 7: DISORDERS OF THE EYES & LIDS		
Optic Neuritis	194	• Newer therapies include monoclonal antibodies against immune cells and cell-based therapies to deplete or modulate T- and B-cell responses. *Derdelinckx J et al. Int J Mol Sci. [PMID: 34360690]*
CHAPTER 8: OTOLARYNGOLOGY DISORDERS		
Bacterial Rhinosinusitis	220	• Dupilumab, a monoclonal antibody with inhibition of IL-4 and IL-13, is FDA-approved for patients with chronic sinusitis with nasal polyposis. *Hoy SM. Drugs. [PMID: 32240527]*
Sensorineural Hearing Loss	212	• There is emerging evidence that conventional audiometry may not fully capture hearing loss (known as "hidden hearing loss"). Many patients may have subclinical hearing loss. *Drennan WR. Audiol Neurootol. [PMID: 34727540]*
CHAPTER 9: PULMONARY DISORDERS		
Allergic Bronchopulmonary Aspergillosis	266	• For patients with frequent exacerbations, the use of biologic agents, such as anti-IgE (omalizumab), anti-IL-5 (mepolizumab, benralizumab), or anti-IL4 receptor (dupilumab), has been shown to improve outcomes. *Koutsokera A et al. J Cyst Fibros. [PMID: 31405730]*
Bronchial Carcinoid Tumors	291	• The aggressiveness of bronchial carcinoid tumors is determined by the cell histology, with "typical carcinoid," a low-grade tumor, demonstrating a more indolent and favorable course than "atypical carcinoid," an intermediate-grade tumor. Bronchial carcinoid tumor staging follows the same TNM classification as other lung cancers. *Singh S et al. J Thorac Oncol. [PMID: 32663527]*

*See chapter for further details and references.

(continued on following page)

Topic	Page Number	Key New Advances Affecting Clinical Practice*
Screening for Lung Cancer	289	• The USPSTF updated its recommendation for low-dose CT screening. Annual low-dose CT screening for lung cancer is recommended for those at high risk; with high-risk criteria including age 50–80 years, at least a 20 pack-years smoking history, and either current smoking or quit date within past 15 years. Screening should be stopped once 15 years have elapsed since quitting smoking, or if a comorbid condition renders the benefits of screening null. Simulation models developed for the purposes of informing this recommendation found yearly screening with these parameters to be the most efficient in reducing lung-cancer related deaths, although more false-positive test results are expected compared with the original recommendation. *Krist AH et al. JAMA. [PMID: 33687470]*
CHAPTER 10: HEART DISEASE		
Chronic Stable Angina Pectoris (Chronic Coronary Syndromes)	361	• CT-functional fractional reserve (CT-FFR) is approved for clinical use and is endorsed with a level IIa recommendation for intermediate-risk patients with chest pain and no prior history of CAD with a 40–90% stenosis on CT imaging to guide need for revascularization. *Writing Committee Members; Gulati M et al. J Am Coll Cardiol. [PMID: 34756653]*
Heart Failure	408, 409	• The FDA approved sacubitril/valsartan in patients with heart failure and preserved LVEF, particularly for patients with an EF less than 50%, including patients with a mildly reduced EF of 41–49%. • Empagliflozin has been FDA-approved to treat heart failure with reduced LVEF, with or without diabetes; it is the only therapy shown to reduce cardiovascular death or heart failure hospitalization in this population. *McDonagh TA et al. Eur J Heart Fail. [PMID: 35083827]* *Bozkurt B et al. J Card Fail. [PMID: 33663906]*
Infectious Myocarditis	414	• Myocarditis following infection with SARS-CoV-2 infection and following vaccination have been reported in the medical literature. In both scenarios, younger male patients seem to be at highest risk for this overall rare event. *Boehmer TK et al. MMWR Morb Mortal Wkly Rep. [PMID: 34473684]* *Witberg G et al. N Engl J Med. [PMID: 34614329]*
Primary & Secondary Prevention of CHD	358	• The USPSTF issued new guidance on the use of aspirin for primary prevention of cardiovascular events; patients aged 40–49 years should have a shared decision-making conversation regarding the potential risks and benefits of initiating aspirin therapy for primary prevention, and patients aged 60 years or older should not initiate aspirin for primary prevention of CVD. *USPSTF.* *https://www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/file/supporting_documents/aspirin-cvd-prevention-final-rec-bulletin.pdf*
CHAPTER 11: SYSTEMIC HYPERTENSION		
Systemic Hypertension	465	• Most guidelines now recommend the use of home blood pressure monitors in the diagnosis of hypertension. The availability of blood pressure profiles generated from multiple home-gathered data points over continuous intervals allows more precise control of the overall hypertensive burden. *Milani RV et al. Curr Opin Cardiol. [PMID: 33871402]*
CHAPTER 12: BLOOD VESSEL & LYMPHATIC DISORDERS		
Aortic Dissection	487	• For patients who cannot tolerate a beta-blocker or who need a second agent to control hypertension, intravenous calcium channel blocker infusions such as nicardipine are an alternative. Start nicardipine 5 mg/hour intravenously and titrate the infusion to the desired effect. *Bossone E et al. Nat Rev Cardiol. [PMID: 33353985]*
Occlusive Disease: Femoral & Popliteal Arteries	475	• Dual treatment with rivaroxaban 2.5 mg orally twice daily and aspirin 81 mg orally daily has been shown to reduce limb-related events, major amputation, and cardiovascular events in patients with femoral and popliteal artery atherosclerosis. *Bauersachs RM et al. J Am Coll Cardiol. [PMID: 34010631]*

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 13: BLOOD DISORDERS		
Plasma Cell Myeloma	538	• For patients with multi-agent refractory disease, chimeric antigen receptor T-cell therapy targeting the early plasma cell antigen BCMA has shown response rates exceeding 70% and median duration of response of over 11 months. *van de Donk NWCJ et al. Lancet Haematol. [PMID: 34048683]*
CHAPTER 14: DISORDERS OF HEMOSTASIS, THROMBOSIS & ANTITHROMBOTIC THERAPY		
Antithrombotic Therapy	563	• For patients with morbid obesity, standard doses of apixaban or rivaroxaban should be chosen rather than using dabigatran or edoxaban. • DOACs are not recommended for VTE treatment in the acute setting following bariatric surgery but can be considered for ongoing treatment after the initial 4 weeks of therapy.
	571	• Heparins may be preferable as initial therapy in hospitalized patients with clinical instability and fluctuating renal or hepatic function, when bleeding risk is high, or when there is concern that thrombolysis may be required. *Stevens SM et al. Chest. [PMID: 34352278]*
Primary VTE Prevention & Treatment in Severe COVID-19	578	• Therapeutic dosing of anticoagulation may benefit some patients who are hospitalized in the acute care setting with COVID-19, who have very elevated D-dimer values and require supplemental oxygen, and who have low bleeding risk. • Patients who are critically ill in ICUs have not been shown to benefit from therapeutic dosing of anticogulation. • There is no clear benefit from VTE prophylaxis for patients with COVID-19 who do not require hospitalization. *ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators; Lawler PR et al. N Engl J Med. [PMID: 34351721]* *REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators; Goligher EC et al. N Engl J Med. [PMID: 34351722]* *Spyropoulos AC. JAMA Intern Med. [PMID: 34617959]*
CHAPTER 15: GASTROINTESTINAL DISORDERS		
Acute Diarrhea	591	• Immune checkpoint inhibitor therapy for malignancies may cause mild to severe GI side effects in 8–27% of patients. *Dougan M et al. Gastroenterology. [PMID: 33080231]* *Siciliano V et al. Rev Recent Clin Trials. [PMID: 32598272]*
	592	• Patients with severe diarrhea or dysentery and a known history of IBD or prior immune checkpoint inhibitor therapy require expedited evaluation with stool studies and possible sigmoidoscopy or colonoscopy with biopsy to exclude infection prior to therapy with intravenous corticosteroids. • Shiga-toxin–producing *Escherichia coli* infection should not be treated with antibiotics due to an increased risk of hemolytic-uremic syndrome, especially in children. *Dougan M et al. Gastroenterology. [PMID: 33080231]* *Siciliano V et al. Rev Recent Clin Trials. [PMID: 32598272]*
Anorectal Infections	670	• Nucleic acid amplification testing for gonorrhea and chlamydia has excellent sensitivity and specificity and is preferred in most clinical settings. *Workowski KA et al. MMWR Recomm Rep. [PMID: 34292926]*
Chronic Diarrhea	594	• Elevated fasting levels (> 48 ng/mL) of the bile acid precursor 7αC4 are strongly predictive of bile acid diarrhea. *Borup C et al. Am J Gastroenterol. [PMID: 32740083]*
Gastrointestinal Hemorrhage	630	• Endoscopic application of a topical hemostatic powder (Hemospray) may provide temporary hemostasis for up to 24 hours in patients with massive bleeding that interferes with effective application of thermocoagulation or endoclip placement. *Hussein M et al. Endoscopy. [PMID: 32459010]*
Inflammatory Bowel Disease	651	• Ozanimod is FDA-approved for the treatment of moderate to severe ulcerative colitis. *Sandborn WJ et al. N Engl J Med. [PMID: 34587385]*

*See chapter for further details and references.

(continued on following page)

Topic	Page Number	Key New Advances Affecting Clinical Practice*
Irritable Bowel Syndrome (IBS)	646	• Peppermint oil may be useful to relieve global IBS symptoms and abdominal pain. *Lacy BE et al. Am J Gastroenterol. [PMID: 33315591]*
	647	• Probiotics are not recommended for IBS treatment. *Lacy BE et al. Am J Gastroenterol. [PMID: 33315591]*
Other Primary Esophageal Motility Disorders	620	• Opioids may exacerbate esophageal dysmotility and should be discontinued, if possible. No medications have been shown to improve symptoms in patient with esophageal hypomotility. *DeLay K et al. Clin Gastroenterol Hepatol. [PMID: 34405804]*
Peptic Ulcer Disease	627	• Commercial laboratories now offer culture-based and molecular-based susceptibility testing for *Helicobacter pylori*, which may be helpful for patients who have failed an initial empiric course of treatment. *Graham DY. Gastroenterology. [PMID: 33647279]*
Zenker Diverticulum	615	• Minimally invasive intraluminal approaches that use flexible endoscopes or rigid esophagoscopes are preferred when symptomatic patients require cricopharyngeal myotomy. *Jirapinyo P et al. Gastrointest Endosc. [PMID: 33926711]*
CHAPTER 16: LIVER, BILIARY TRACT, & PANCREAS DISORDERS		
Cirrhosis	702	• In patients with clinically significant portal hypertension, carvedilol, a nonselective beta-receptor antagonist with alpha-1 blocking activity, appears to reduce the frequency of decompensating events, although it may lead to hypotension particularly in patients with decompensated cirrhosis. *Tandon P et al. Clin Gastroenterol Hepatol. [PMID: 33221550]*
	703	• Vancomycin should be added in patients with prior bacterial peritonitis or a positive surveillance swab for methicillin-resistant *Staphylococcus aureus*. Daptomycin should be added in patients with a positive surveillance swab for vancomycin-resistant enterococcus. Meropenem can be used in patients with current or recent exposure to piperacillin-tazobactam. *Biggins SW et al. Hepatology. [PMID: 33942342]*
Hemochromatosis	710	• Serum biomarkers of fibrosis may be an alternative to liver biopsy for identifying advanced fibrosis. *Chin J et al. Clin Gastroenterol Hepatol. [PMID: 32745684]*
Nonalcoholic Fatty Liver Disease	698	• Noninvasive approaches to the assessment of fibrosis are now preferred, with liver biopsy reserved when results of noninvasive testing are inconclusive. The FIB-4 score is often used particularly to exclude advanced fibrosis because of its simplicity. It is based on age, platelet count, and serum AST and ALT levels. *Younossi ZM et al. Am J Gastroenterol. [PMID: 33284184]*
Primary Biliary Cholangitis	708	• Obeticholic acid, a farnesoid X receptor agonist, can cause serious liver injury in patients with advanced cirrhosis, and its use in these patients has been restricted by the FDA. *Lleo A et al. Lancet. [PMID: 33308474]*

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 17: BREAST DISORDERS		
Carcinoma of the Female Breast	752	• Olaparib has been shown to reduce the relative risk of an invasive recurrence for *BRCA1/2* carriers with high-risk disease; abemaciclib has been shown to improve the invasive disease-free survival for those with high-risk HR-positive disease; pembrolizumab has been shown to improve the event-free survival for patients with stage II or greater triple-negative breast cancer. *Schmid P et al; KEYNOTE-522 Investigators. N Engl J Med. [PMID: 32101663]* *Tutt ANJ et al; OlympiA Clinical Trial Steering Committee and Investigators. N Engl J Med. [PMID: 34081848]*
	754	• Hormonally driven breast cancer may be particularly sensitive to inhibition of cell cycle regulatory proteins, called cyclin dependent kinases 4 and 6 (CDK 4/6). Three oral CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—are FDA-approved for treatment of HR-positive, HER2-negative metastatic breast cancer. • Two poly(ADP-ribose) polymerase (PARP) inhibitors (olaparib and talazoparib) are FDA-approved for the treatment of BRCA-associated metastatic breast cancer. The NCCN guidelines include adjuvant olaparib for select patients and recommend germline genetic testing for any patient who may be a candidate for adjuvant olaparib. *Schmid P et al; KEYNOTE-522 Investigators. N Engl J Med. [PMID: 32101663]* *Tutt ANJ et al; OlympiA Clinical Trial Steering Committee and Investigators. N Engl J Med. [PMID: 34081848]*
CHAPTER 18: GYNECOLOGIC DISORDERS		
Intrauterine Devices	778	• The levonorgestrel 52-mg intrauterine device can be inserted within 5 days following a single episode of unprotected midcycle coitus as a postcoital contraceptive. *Turok DK et al. N Engl J Med. [PMID: 33503342]*
Pelvic Inflammatory Disease (Salpingitis, Endometritis)	786	• The recommended outpatient regimen is ceftriaxone (500 mg intramuscularly; 1 g for persons who weigh 150 kg or greater) plus doxycycline (100 mg orally twice a day for 14 days) with metronidazole 500 mg orally twice a day or a single dose of cefoxitin (2 g intramuscularly) with probenecid (1 g orally) plus doxycycline (100 mg orally twice daily for 14 days) and metronidazole 500 mg orally twice daily for 14 days. *Workowski KA et al. MMWR Recomm Rep. [PMID: 34292926]*
CHAPTER 19: OBSTETRICS & OBSTETRIC DISORDERS		
Cholelithiasis & Cholecystitis	817	• The most common cause of acute pancreatitis in pregnancy is gallstone disease. The diagnosis can be confirmed with an appropriate history and an elevated serum amylase or lipase. Management is conservative, including bowel rest, intravenous fluids, supplemental nutrition if necessary, and analgesics. CT imaging should be avoided unless severe complications are suspected. *Abushamma S et al. Obstet Gynecol. [PMID: 34011887]*
Immunizations During Pregnancy	795	• Vaccination against COVID-19 is recommended for women who are pregnant, trying to get pregnant or may become pregnant, and who are breastfeeding. The CDC has determined that the benefits of vaccination outweigh any risks. There is no evidence that vaccination causes problems with fertility in men or women. Pregnant women who have been vaccinated may receive the COVID-19 booster shot. There have been rare reports of thrombosis with thrombocytopenia syndrome in women younger than 50 years old who received the Johnson and Johnson's Janssen vaccine. This risk has not been found with the Pfizer-BioNTech and Moderna vaccines; women younger than 50 years old with access to multiple vaccines may want to factor this into their decision-making process. *CDC. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html*
Maternal Hepatitis B & C Carrier State	816	• Universal screening for hepatitis C virus in pregnancy is recommended. Direct-acting antiviral regimens should only be initiated during pregnancy if in the setting of a clinical trial. Cesarean section is not recommended solely for a maternal history of hepatitis C. During labor, early rupture of membranes and placement of a fetal scalp electrode should be avoided if safe to do so. *Dotters-Katz SK et al. Am J Obstet Gynecol. [PMID: 34116035]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
Preterm Labor	805	• The recommended regimen for antimicrobial prophylaxis against group B streptococcus is penicillin G, 5 million units intravenously as a loading dose and then 2.5–3 million units intravenously every 4 hours until delivery. In penicillin-allergic patients not at high risk for anaphylaxis, 2 g of cefazolin can be given intravenously as an initial dose and then 1 g intravenously every 8 hours until delivery. In patients at high risk for anaphylaxis, vancomycin, 20 mg/kg intravenously every 8 hours until delivery, can be used. Clindamycin, 900 mg intravenously every 8 hours until delivery, can also be used after a group B streptococcal isolate has been confirmed to be susceptible to clindamycin. *American College of Obstetricians and Gynecologists. Obstet Gynecol. [PMID: 34794160]*
CHAPTER 20: RHEUMATOLOGIC, IMMUNOLOGIC, & ALLERGIC DISORDERS		
Complex Regional Pain Syndrome	867	• Vitamin C supplementation may have a role in preventing the development of complex regional pain syndrome following surgical procedures known to be a risk factor. *Jacques H et al. Int Orthop. [PMID: 33438072]*
Gonococcal Arthritis	863	• The treatment of disseminated gonorrhea is parenteral ceftriaxone. Once susceptibility testing has been obtained, 24–48 hours after clinical improvement the antibiotic regimen can be changed to an oral agent to complete a 7-day course. *CDC. https://www.cdc.gov/std/treatment-guidelines/gonorrhea-adults.htm*
Granulomatosis with Polyangiitis	853	• American College of Rheumatology/Vasculitis Foundation recommendations favor rituximab as first-line induction therapy. Cyclophosphamide may also be used for induction therapy. Avacopan is FDA-approved as add-on treatment for severe ANCA-associated vasculitis induction therapy in combination with rituximab or cyclophosphamide plus corticosteroids. • For nonsevere disease without life- or organ-threatening manifestations, methotrexate up to 25 mg oral or subcutaneous weekly plus corticosteroids may be effective induction therapy. • Rituximab, dosed at a fixed interval of 1 g every 6 months or 500 mg every 4 months, is favored as first-line maintenance treatment. *Chung SA et al. Arthritis Rheumatol. [PMID: 34235894]* *Jayne DRW et al; ADVOCATE Study Group. N Engl J Med. [PMID: 33596356]*
Polyarteritis Nodosa	851	• High-dose pulse methylprednisolone is recommended as the initial treatment for severe polyarteritis nodosa. *Chung SA et al. Arthritis Rheumatol. [PMID: 34235883]*
Relapsing Polychondritis	856	• A newly described genetic syndrome, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic), is caused by somatic mutations in *UBA1* in hematopoietic progenitor cells. Clinical features include hematologic manifestations (cytopenias, bone marrow failure) and a spectrum of inflammatory features such as chondritis, vasculitis, fever, and arthritis. This rare syndrome (predominately in males because it is X-linked) should be considered in the differential diagnosis of chondritis especially in the presence of an unexplained macrocytosis and evidence of systemic inflammation (ie, high ESR/CRP). *Ferrada MA et al. Arthritis Rheumatol. [PMID: 33779074]*
Rheumatoid Arthritis	831	• Because rituximab reduces the humoral immune response, it should be used with caution during the COVID-19 pandemic as multiple studies suggest a higher risk of mortality from COVID-19 in patients using this medication. *Fraenkel L et al. Arthritis Care Res (Hoboken). [PMID: 34101387]*
Systemic Lupus Erythematosus	835–836	• Belimumab is FDA-approved for the treatment of active lupus nephritis. • Anifrolumab, a type 1 interferon receptor antagonist, is FDA-approved to treat non-renal lupus that has not responded to standard therapies. • Voclosporin, a novel calcineurin inhibitor, is FDA-approved to treat active lupus nephritis when used in combination with mycophenolate mofetil. • Evidence increasingly suggests that renal response can be enhanced with combination immunosuppressive therapy. *Morand EF et al; TULIP-2 Trial Investigators. N Engl J Med. [PMID: 31851795]* *Rovin BH et al. Lancet. [PMID: 33971155]*

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
Systemic Sclerosis (Scleroderma)	841	• Tocilizumab, an IL-6 inhibitor, slows the rate of decline in pulmonary function and may be used as an alternative for patients who cannot tolerate mycophenolate mofetil. Azathioprine is an additional option for treatment of systemic sclerosis–associated lung disease. *Khanna D et al; focuSSced Investigators. Lancet Respir Med. [PMID: 32866440]*
CHAPTER 21: ELECTROLYTE & ACID-BASE DISORDERS		
Hyperkalemia	886	• Small studies have suggested the utility of patiromer and sodium zirconium cyclosilicate in acute hyperkalemia; if administered for hyperkalemic emergency, sodium zirconium cyclosilicate is preferred due to its more rapid onset of action. *Rafique Z et al. Acad Emerg Med. [PMID: 31599043]* *Peacock WF et al. Acam Emerg Med. [PMID: 32149451]*
CHAPTER 22: KIDNEY DISEASE		
Diabetic Nephropathy	935	• Mineralocorticoid receptor antagonism can be considered for blood pressure and proteinuria management in type 2 diabetes mellitus with careful monitoring for hyperkalemia. *Hahr AJ et al. Am J Kidney Dis. [PMID: 34600745]*
IgA Nephropathy	927	• SGLT2-inhibitors may be added to standard care in the well-selected patient. There are conflicting data regarding the efficacy of corticosteroids for reducing proteinuria and slowing progression; however, they may be considered for patients with GFR greater than 30 mL/ minute/1.73 m^2 and persistent proteinuria greater than 1 g/day despite maximal ACE inhibitor or ARB. *Cheung CK et al. J Clin Med. [PMID: 34200024]*
CHAPTER 24: NERVOUS SYSTEM DISORDERS		
Dementia	1016	• Aducanumab was approved by the FDA despite mixed results in clinical trials. Its use is limited to patients with mild cognitive impairment or mild dementia and amyloid pathology proven by amyloid PET. The ultimate role of this medication is still being debated.
Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)	1005	• Weight loss is important: bariatric surgery led to a decrease in both intracranial pressure and weight at 2 years compared with a community weight management program in a randomized trial and may be considered in patients with a BMI of 35 or greater. *Mollan SP et al. JAMA Neurol. [PMID: 33900360]*
Metastatic Intracranial Tumors	1001	• Memantine (5 mg once daily orally titrated by 5 mg weekly to 10 mg twice daily) reduced cognitive toxicity associated with whole-brain radiotherapy in a randomized trial and is recommended; this effect can be augmented through intensity modulated radiation therapy with hippocampal avoidance. *Brown PD et al. J Clin Oncol. [PMID: 32058845]*
Muscular Dystrophies	1044	• Casimersen is FDA-approved for treatment of Duchenne muscular dystrophy; it shows benefit in patients with a mutation amenable to exon 45 skipping.
Transient Ischemic Attack (TIA)	987	• Dual antiplatelet therapy with aspirin and clopidogrel is recommended for 90 days after a TIA or stroke due to 70–99% stenosis of an intracranial artery. • The left atrial appendage is the source of embolism in most patients with atrial fibrillation. Several randomized trials showed percutaneous left atrial appendage closure was equivalent to anticoagulation in preventing stroke and systemic embolization, and several devices are approved for this indication in the United States and Europe. The procedure should be considered in patients with a contraindication to long-term anticoagulation, although short-term anticoagulation (45 days) followed by dual antiplatelet therapy (4.5 months) and then indefinite aspirin monotherapy is usually necessary after device placement. *Kleindorfer DO et al. 2021 Stroke. [PMID: 34024117]*
CHAPTER 25: PSYCHIATRIC DISORDERS		
Psychosexual Disorders	1059	• Bremelanotide is FDA-approved for the treatment of hypoactive sexual desire disorder in premenopausal women; however, the mechanism of action is unclear and subjective improvement is low. *Wheeler LJ et al. Obstet Gynecol. [PMID: 32541291]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
Somatic Symptom Disorders (Abnormal Illness Behavior)	1055	• Physical-based therapies such as speech/occupational/physical have strong evidence for improving symptoms in those suffering from functional neurologic disorder. *Gilmour GS et al. J Neurol. [PMID: 32193596]*
Trauma & Stressor-related Disorders	1048	• MDMA (methylenedioxymethamphetamine, also called ecstasy) significantly enhanced the treatment effects associated with manualized therapy for severe PTSD. *Mitchell JM et al. Nat Med. [PMID: 33972795]*
CHAPTER 28: LIPID DISORDERS		
Treatment of High LDL Cholesterol	1247	• The FDA approved the novel PCSK9 inhibitor inclisiran, which uses silencing RNA technology to reduce liver production of PCSK9 protein by approximately 80%. Twice-yearly dosing is novel for lipid-lowering therapy; inclisiran enables new delivery strategies, including in-clinic administration. *Raal FJ et al; ORION-9 Investigators. N Engl J Med. [PMID: 32197277]* *Ray KK et al; ORION-10 and ORION-11 Investigators. N Engl J Med. [PMID: 32187462]*
CHAPTER 29: NUTRITIONAL DISORDERS & OBESITY		
Obesity	1257	• Semaglutide, a GLP-1 receptor agonist, is FDA-approved for the treatment of obesity. *Wilding JPH et al. N Engl J Med. [PMID: 33567185]*
CHAPTER 30: COMMON PROBLEMS IN INFECTIOUS DISEASES & ANTIMICROBIAL THERAPY		
Infections in the Immunocompromised Patient	1276	• While the traditional approach was to continue antibiotics until resolution of neutropenia, current evidence supports earlier discontinuation of antibiotics in the neutropenic patient who becomes afebrile for 72 hours, if no signs or symptoms of infection persist.
CHAPTER 31: HIV INFECTION & AIDS		
HIV Infection & AIDS	1329	• In the ANCHOR study, which involved nearly 4500 individuals with anal high-grade squamous intraepithelial lesions (HGSIL), nine patients who were assigned to aggressive therapy (mostly office-based electrocautery) developed anal cancer compared with 21 of those in an active monitoring group, representing a 57% decrease in relative risk over the median 25.8-month follow-up period. This pivotal study will change care toward more aggressive screening for HGSIL and treatment to prevent progression to anal cancer. *Palefsky J et al. CROI 2022 (special session).*
	1332	• Cabotegravir was FDA-approved for use as preexposure prophylaxis as an injectable medication, every 8 weeks. This medication has been shown to be superior to oral tenofovir disoproxil fumarate/emtricitabine in preventing HIV infection among men who have sex with men, transgender women who have sex with men, and cisgender women in sub-Saharan Africa.
	1337	• Prophylaxis against *Mycobacterium avium* complex is no longer recommended in most individuals who are initiating antiretroviral therapy (ART), including in those with CD4+ counts less than 50 cells/mcL. The incidence of *M avium* complex infection is very low among those on ART.
	1338	• The TEMPRANO trial showed that individuals immediately initiating ART versus delaying treatment for CD4 count to fall below 500 cells/mcL had lower rates of severe illness.

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 32: VIRAL & RICKETTSIAL INFECTIONS		
Ebola Viral Disease	1390	• The World Health Organization recommends automated or semi-automated nucleic acid tests (NATs) of EDTA-anticoagulated whole blood from symptomatic patients for routine diagnostic management, and rapid antigen detection tests in areas where NATs are not available. Oral fluid can be used for diagnostics when blood collection is not possible. *Choi MJ et al. MMWR Recomm Rep. [PMID: 33417593]*
Japanese Encephalitis	1382	• At least eight effective types of vaccine against Japanese encephalitis are available worldwide, including live attenuated and inactivated vaccines. *Kwak BO et al. Vaccine. [PMID: 33712352]*
Poliomyelitis	1375	• A novel oral polio vaccine type 2 (nOPV2) has been developed in response to the ongoing circulating vaccine-derived type 2 poliovirus outbreaks and has been shown to be safe and immunogenic in previously immunized adults. Studies have shown that nOPV2 is more genetically stable than the mOPV2 and therefore less prone to reverting to neurovirulence. The nOPV2 was recommended for initial use under the World Health Organization's Emergency Use Listing Procedure in November 2020. *Coster ID et al. Lancet. [PMID: 33308429]*
Severe Acute Respiratory Syndrome—COVID-19 (SARS-COV-2)	1401	• *CMDT* updates the ever-evolving knowledge of SARS-CoV-2 and the related disease online at www.accessmedicine.com
Tick-borne Encephalitis (TBE)	1383	• TicoVac (known as FSME-Immun in Europe) was FDA-approved. The vaccine is indicated for those residing and traveling to endemic areas (and the disease is now extending to higher altitudes with climate change). *Ličková M et al. Ticks Tick Borne Dis. [PMID: 32173297]*
CHAPTER 34: SPIROCHETAL INFECTIONS		
Lyme Disease (Lyme Borreliosis)	1493	• When assessing for CNS Lyme disease in an appropriate clinical syndrome, serum antibody testing is recommended over cerebrospinal fluid serology or PCR. • While serology is recommended to diagnose Lyme arthritis, PCR can be done on synovial fluid or tissue if needed to confirm the diagnosis and guide treatment. *Lantos PM et al. Clin Infect Dis. [PMID: 33417672]*
CHAPTER 35: PROTOZOAL & HELMINTHIC INFECTIONS		
African Trypanosomiasis (Sleeping Sickness)	1497	• Fexinidazole is recommended by the World Health Organization as first-line therapy and is FDA-approved for treatment of early and advanced (CNS) West African disease. *Hidalgo J et al. Cureus. [PMID: 34513456]*
Leishmaniasis	1501	• Alternative therapies increasingly used to treat cutaneous leishmaniasis are miltefosine, which benefits from oral dosing and relatively little toxicity, and amphotericin B, which is widely available. *Machado PRL et al. Clin Infect Dis. [PMID: 32894278]*
Malaria	1507	• Artemisinin resistance is mediated by any of a series of mutations in the *Plasmodium falciparum* kelch (K13) gene; of great concern, these same mutations and evidence for delayed clearance after treatment with artemisinins were reported in East Africa in 2021. *Balikagala B et al. N Engl J Med. [PMID: 34551228]*
CHAPTER 36: MYCOTIC INFECTIONS		
Candidiasis	1535	• Oral ibrexafungerp, a highly bioavailable glucan synthase inhibitor, may be used to treat vulvovaginal candidiasis from any disease-causing *Candida* strains, including azole-resistant pathogens. *Gold JAW et al. Clin Infect Dis. [PMID: 34079987]*

*See chapter for further details and references.

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Topic	Page Number	Key New Advances Affecting Clinical Practice*
CHAPTER 38: POISONING		
Marijuana & Synthetic Cannabinoids	1585	• Cannabidiol (CBD) is a constituent of Cannabis that does not produce THC-like intoxication. CBD extracts are available over the counter and via the internet for a variety of proposed effects (anti-inflammatory, antioxidant, anxiolysis) and by prescription for some pediatric seizure disorders. Overdoses are typically not dangerous. *Alves VL et al. Crit Rev Toxicol. [PMID: 32530350]*
Theophylline & Caffeine	1592	• Hemodialysis has been used in patients with caffeine overdose. • Extracorporeal membrane oxygenation has been used successfully in hemodynamic collapse after caffeine overdose. *Ou HC et al. Am J Emerg Med. [PMID: 34922795]* *Yasuda S et al. Acute Med Surg. [PMID: 33532077]*
CHAPTER 39: CANCER		
Bladder Cancer	1644	• Pembrolizumab is FDA-approved for patients with high-risk, non–muscle invasive bladder cancers who have failed intravesical bacillus Calmette–Guérin therapy. Nivolumab has also been approved in the adjuvant setting after radical cystectomy or nephroureterectomy for urothelial carcinoma at high risk for recurrence. • The fibroblast growth factor receptor inhibitor erdafitinib is approved after initial therapy for patients with progressive metastatic urothelial carcinoma whose tumors harbor these mutations with expected response rates of up to 40%. • Enfortumab vedotin is the first antibody-drug conjugate approved for advanced and metastatic urothelial carcinoma. The antibody targets Nectin-4 and demonstrates a 44% response rate (including 12% complete response) in patients who have progressed after multiple other lines of therapy. *Bajorin DF et al. N Engl J Med. [PMID: 34077643]* *Balar AV et al. Lancet Oncol. [PMID: 34051177]* *Rosenberg JE at al. J Clin Oncol. [PMID: 31356140]*
Bronchogenic Carcinoma	1606–1607	• The FDA approved sotorasib (AMG 510) for the treatment of *KRAS* G12C mutated lung cancers after progression on first-line treatment. • Atezolizumab (PD-L1 inhibitor) can be given for 1 year post–adjuvant chemotherapy for resected stage II to IIIA NSCLC, based on a phase 3 trial showing improvement in disease-free survival compared with adjuvant chemotherapy without atezolizumab. For stage III NSCLCs, a phase 3 trial has shown improved survival outcomes by adding durvalumab (PD-L1 inhibitor) as consolidation therapy post–definitive chemoradiation. • Five-year follow-up data for patients with 50% or greater PD-L1 expression show that patients who received pembrolizumab versus chemotherapy alone had improved median overall survival of 26 months versus 13 months. *Skoulidis F et al. N Engl J Med. [PMID: 34096690]* *Reck M et al. J Clin Oncol. [PMID: 33872070]* *Felip E et al. Lancet. [PMID: 34555333]*
Colorectal Cancer (CRC)	1630	• For the 50% of patients with metastatic CRC who have *KRAS/NRAS/BRAF* wild-type tumors, cetuximab and panitumumab (monoclonal antibodies to the epithelial growth factor receptor), in combination with chemotherapy, can extend median survival by 2 to 4 months compared with chemotherapy alone. For the 5% to 10% with BRAF V600E sequence variations, targeted combination therapy with BRAF and EGFR inhibitors extend overall survival to 9.3 months, compared with 5.9 months for those receiving standard chemotherapy.
	1633	• In four randomized clinical trials (n = 458,002), intention to screen with 1- or 2-time flexible sigmoidoscopy versus no screening was associated with a significant decrease in CRC–specific mortality. *National Comprehensive Cancer Network.* *https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf* *National Comprehensive Cancer Network.* *https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf* *Shaukat A et al. Am J Gastroenterol. [PMID: 33657038]*

*See chapter for further details and references.

Topic	Page Number	Key New Advances Affecting Clinical Practice*
Esophageal Cancer	1618	• For patients who complete neoadjuvant chemoradiation and undergo a complete resection but are found to have residual cancer in the resection specimen, a year of adjuvant immunotherapy with nivolumab is recommended. *Ahmed O et al. Clin Gastroenterol Hepatol. [PMID: 33813072]*
Gastric Adenocarcinoma	1621	• Triplet chemotherapy for resectable gastric cancer is recommended for patients who are fit but is associated with more toxicity than doublet chemotherapy.
	1622	• The development of immunotherapy represents a promising strategy in a selected patients with locally advanced and metastatic gastric cancer. Testing for microsatellite instability-high (MSI-H), mismatch repair deficiency (dMMR), PD-1, and PD-L1 is recommended in advanced disease to identify tumors that may respond to immunotherapy. *ASGE Standards of Practice Committee; Jue TL et al. Gastrointest Endosc. [PMID: 33168194]* *de Steur WO et al; CRITICS investigators. Ann Oncol. [PMID: 33227408]* *Kawazoe A et al. Jpn J Clin Oncol. [PMID: 33241322]* *Ng SP et al. Ann Surg Oncol. [PMID: 33689079]*
Malignancies of the Small Intestine	1625	• For advanced/unresectable disease, first-line doublet chemotherapy is standard. Two trials suggest value from adding bevacizumab to chemotherapy. Pembrolizumab is an accepted treatment modality for mismatch repair-deficient tumors. *National Comprehensive Cancer Network.* *https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf*
Prostate Cancer	1635	• Multiparametric MRI (mpMRI) has emerged as the imaging study of choice for localized prostate cancer detection and characterization. Suspicious prostatic lesions may then be sampled via MRI-guided needle biopsy or via MR Fusion (in which prostate MRI images are fused in real-time with images from an ultrasound-guided needle biopsy). Such an approach may improve discovery of potentially life-threatening disease while limiting over-detection of indolent prostate cancer or unnecessary prostate biopsies. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1637	• NCCN guidelines recommend considering germline genetic testing in men presenting with localized high-risk, regionally advanced, or metastatic disease. Commercially available cancer tissue RNA-based assays are available for further risk assessment after prostate cancer diagnosis; these may help determine the need for and timing of prostate cancer treatment as well as treatment intensity. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1637	• A secondary data analysis from the Prostate, Lung, Colorectal, and Ovarian trial demonstrated that baseline PSA for younger men in their 50s can predict long-term risk of prostate cancer and can be used to tailor PSA screening intervals. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1638	• Active surveillance is now the preferred initial treatment recommendation for men with well-differentiated prostate cancer and low-risk clinical features. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1641	• Results from the PEACE-1 trial demonstrate that a three-drug regimen, with androgen deprivation therapy, docetaxel and abiraterone acetate used together, provides the best survival outcome for men with hormone-naïve metastatic cancer. With this regimen, the median survival for men with de novo metastatic prostate cancer is now expected to be 5 years. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*
	1641	• Poly(ADP-ribose) polymerase (PARP) inhibitors represent a novel class of anticancer agents with some activity against prostate cancer, particularly those harboring mutations in genes important for homologous recombination such as *BRCA1*, *BRCA2*, and *ATM*. There are two FDA-approved PARP inhibitors available for men with metastatic castrate-resistant prostate cancer with these genetic alterations. *Kovac E et al. JAMA Netw Open. [PMID: 31940039]*

*See chapter for further details and references.

(continued on following page)

Topic	Page Number	Key New Advances Affecting Clinical Practice*
Renal Cell Carcinoma	1646	• For patients with von Hippel-Lindau disease and renal cell carcinoma, belzutifan, a HIF2a inhibitor, leads to dramatic size reductions in both renal and non-renal neoplasms and offers a new treatment option. • Pembrolizumab is FDA-approved for adjuvant treatment after surgical resection of renal cell carcinoma in patients at high risk for disease recurrence. • The SURTIME randomized trial compared immediate versus deferred cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with sunitinib and showed an overall survival advantage with the deferred approach. This may serve to identify patients who respond the best to systemic therapy prior to undergoing removal of the primary tumor. *Bex A et al. JAMA Oncol. [PMID: 30543350]* *Jonasch E et al. N Engl J Med. [PMID: 34818478]* *Rini BI et al; KEYNOTE-426 Investigators. N Engl J Med. [PMID: 30779529]*
Toxicity & Dose Modification of Chemotherapeutic Agents	1657	• The main toxicities of immune checkpoint inhibitors involve immune-related adverse events which occur via the same mechanisms as their antitumor effects (ie, self-reactive T-cells escaping central tolerance). The combination of PD-1 or PD-L1 inhibitors with CTLA-4 inhibitors results in higher rates of grade 3 or higher and all grades of immune-related adverse events. *Brahmer JR et al. J Immunother Cancer. [PMID: 34172516]*
CHAPTER 41: ORTHOPEDIC DISORDERS & SPORTS MEDICINE		
Dupuytren Contracture	1691	• Some evidence suggests superior clinical outcomes of percutaneous needle aponeurotomy for Dupuytren Contracture compared with collagenase *Clostridium histolyticum* (CCH) injections and a higher minor complication rate with CCH. *Hirase T et al. J Hand Microsurg. [PMID: 34511831]*
Low Back Pain	1685	• Heat treatments have shown to have short-term benefits for acute low back pain. • There is good evidence that spinal manipulation and acupuncture provide short-term improvement compared with usual care alone. • Intra-articular steroid injections and cooled radiofrequency ablation of the sacral lateral branch nerves and dorsal ramus of L5 can be considered for patients with persistent sacroiliac joint pain. There is fair evidence that thermal radiofrequency ablation of the facet joints improves pain for at least 6 months. *Kreiner DS et al. Spine J. [PMID: 32333996]*
CHAPTER 42: SEXUAL, GENDER, & MINORITY HEALTH		
Health Care for Lesbian & Bisexual Women	1718	• One study of 150 lesbian, bisexual, and queer women offered preliminary evidence that social support, resilience, and self-esteem help foster body appreciation, which might be protective against mental health concerns and disordered eating.
	1714	• A report demonstrated significantly better reproductive outcomes after reciprocal in vitro fertilization (IVF), with a clinical pregnancy rate of 60% compared with 40% after autologous IVF, and live birth rate of 57.1% in reciprocal IVF versus 29.8% in autologous IVF. However, both partners of the couple need to be willing to participate in reciprocal IVF. *Burnette CB et al. Health Equity. [PMID 31289784]* *Núñez A et al. LGBT Health. [PMID: 34061679]*

*See chapter for further details and references.

Disease Prevention & Health Promotion

1

Michael Pignone, MD, MPH[1]
René Salazar, MD

GENERAL APPROACH TO THE PATIENT

The medical interview serves several functions. It is used to collect information to assist in diagnosis (the "history" of the present illness), to understand patient values, to assess and communicate prognosis, to establish a therapeutic relationship, and to reach agreement with the patient about further diagnostic procedures and therapeutic options. It also serves as an opportunity to influence patient behavior, such as in motivational discussions about smoking cessation or medication adherence. Interviewing techniques that avoid domination by the clinician increase patient involvement in care and patient satisfaction. Effective clinician-patient communication and increased patient involvement can improve health outcomes.

Patient Adherence

For many illnesses, successful prevention and treatment depends on difficult fundamental behavioral changes, including altering diet, taking up exercise, giving up smoking, cutting down drinking, wearing masks to prevent infection, and adhering to medication regimens that are often complex. Adherence is a problem in every practice; up to 50% of patients fail to achieve full adherence, and one-third never take their medicines. Many patients with medical problems, even those with access to care, do not seek appropriate care or may drop out of care prematurely. Adherence rates for short-term, self-administered therapies are higher than for long-term therapies and are inversely correlated with the number of interventions, their complexity and cost, and the patient's perception of overmedication.

As an example, in HIV-infected patients, adherence to antiretroviral therapy is a crucial determinant of treatment success. Studies have unequivocally demonstrated a close relationship between patient adherence and plasma HIV RNA levels, CD4 cell counts, and mortality. Adherence levels of more than 95% are needed to maintain virologic suppression. However, studies show that 40% of patients are less than 90% adherent and that adherence tends to decrease over time.

Patient reasons for suboptimal adherence include simple forgetfulness, being away from home, being busy, and changing daily routine. Other reasons include psychiatric disorders (depression or substance misuse), uncertainty about the effectiveness of treatment, lack of knowledge about the consequences of poor adherence, regimen complexity, and treatment side effects. The rising costs of medications, including generic drugs, and the increase in patient cost-sharing burden, have made adherence even more difficult, particularly for those with lower incomes.

Patients seem better able to take prescribed medications than to adhere to recommendations to change their diet, exercise habits, or alcohol intake or to perform various self-care activities (such as monitoring blood glucose levels at home). For short-term regimens, adherence to medications can be improved by giving clear instructions. Writing out advice to patients, including changes in medication, may be helpful. Because low functional health literacy is common (almost half of English-speaking US patients are unable to read and understand standard health education materials), other forms of communication—such as illustrated simple text, videotapes, or oral instructions—may be more effective. For non–English-speaking patients, clinicians and health care delivery systems can work to provide culturally and linguistically appropriate health services.

To help improve adherence to long-term regimens, clinicians can work with patients to reach agreement on the goals for therapy, provide information about the regimen, ensure understanding by using the "teach-back" method, counsel about the importance of adherence and how to organize medication-taking, reinforce self-monitoring, provide more convenient care, prescribe a simple dosage regimen for all medications (preferably one or two doses daily), suggest ways to help in remembering to take doses (time of day, mealtime, alarms) and to keep appointments, prescribe lower-cost generic medications when available, and provide ways to simplify dosing (medication boxes). Single-unit doses supplied in foil wrappers can increase adherence but should be avoided for patients who have difficulty opening them. Medication boxes with

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compartments (eg, Medisets) that are filled weekly are useful. Microelectronic devices can provide feedback to show patients whether they have taken doses as scheduled or to notify patients within a day if doses are skipped. Reminders, including cell phone text messages, are another effective means of encouraging adherence. The clinician can also enlist social support from family and friends, recruit an adherence monitor, provide a more convenient care environment, and provide rewards and recognition for the patient's efforts to follow the regimen. Collaborative programs in which pharmacists help ensure adherence are also effective. Motivational interviewing techniques can be helpful when patients are ambivalent about their therapy.

Adherence is also improved when a trusting doctor-patient relationship has been established and when patients actively participate in their care. Clinicians can improve patient adherence by inquiring specifically about the behaviors in question. When asked, many patients admit to incomplete adherence with medication regimens, with advice about giving up cigarettes, or with engaging only in "safer sex" practices. Although difficult, sufficient time must be made available for communication of health messages.

Medication adherence can be assessed generally with a single question: "In the past month, how often did you take your medications as the doctor prescribed?" Other ways of assessing medication adherence include pill counts and refill records; monitoring serum, urine, or saliva levels of drugs or metabolites; watching for appointment nonattendance and treatment nonresponse; and assessing predictable drug effects, such as weight changes with diuretics or bradycardia from beta-blockers. In some conditions, even partial adherence, as with drug treatment of hypertension and diabetes mellitus, improves outcomes compared with nonadherence; in other cases, such as HIV antiretroviral therapy or tuberculosis treatment, partial adherence may be worse than complete nonadherence.

Guiding Principles of Care

Ethical decisions are often called for in medical practice, at both the "micro" level of the individual patient-clinician relationship and at the "macro" level of allocation of resources or the adoption of infection-reducing public health interventions. Ethical principles that guide the successful approach to diagnosis and treatment are honesty, beneficence, justice, avoidance of conflict of interest, and the pledge to do no harm. Increasingly, Western medicine involves patients in important decisions about medical care, eg, which colorectal screening test to obtain or which modality of therapy for breast cancer or how far to proceed with treatment of patients who have terminal illnesses (see Chapter 5).

The clinician's role does not end with diagnosis and treatment. The importance of the empathic clinician in helping patients and their families bear the burden of serious illness and death cannot be overemphasized. "To cure sometimes, to relieve often, and to comfort always" is a French saying as apt today as it was five centuries ago—as is Francis Peabody's admonition: "The secret of the care of the patient is in caring for the patient." Training to improve mindfulness and enhance patient-centered communication increases patient satisfaction and may also improve clinician satisfaction.

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Foley L et al. Prevalence and predictors of medication non-adherence among people living with multimorbidity: a systematic review and meta-analysis. BMJ Open. 2021;11:e044987. [PMID: 34475141]
Peh KQE et al. An adaptable framework for factors contributing to medication adherence: results from a systematic review of 102 conceptual frameworks. J Gen Intern Med. 2021;36:2784. [PMID: 33660211]

HEALTH MAINTENANCE & DISEASE PREVENTION

Preventive medicine can be categorized as primary, secondary, or tertiary. Primary prevention aims to remove or reduce disease risk factors (eg, immunization, giving up or not starting smoking). Secondary prevention techniques promote early detection of disease or precursor states (eg, routine cervical Papanicolaou screening to detect carcinoma or dysplasia of the cervix). Tertiary prevention measures are aimed at limiting the impact of established disease (eg, partial mastectomy and radiation therapy to remove and control localized breast cancer).

Tables 1–1 and 1–2 give leading causes of death in the United States for 2020 and recent estimates of deaths from preventable causes from 2019. The 2020 data demonstrate the large impact of COVID-19 on mortality and continue to show increased mortality rates, generally driven by the effects of COVID-19 as well as increases in deaths from

Table 1–1. Leading causes of death in the United States, 2020.

Category	Estimate
All causes	**3,358,814**
1. Diseases of the heart	690,882
2. Malignant neoplasms	598,932
3. COVID-19	345,323
4. Unintentional injuries	192,176
5. Cerebrovascular diseases	159,050
6. Chronic lower respiratory diseases	151,637
7. Alzheimer disease	133,382
8. Diabetes mellitus	101,106
9. Influenza and pneumonia	53,495
10. Nephritis, nephrotic syndrome, and nephrosis	52,260
11. Intentional self-harm (suicide)	44,834

Data from National Center for Health Statistics, 2021.

Table 1–2. Leading preventable causes of death in the United States, 2019.

Category	Estimate
Tobacco	546,401
High blood pressure	495,201
High fasting plasma glucose	439,212
Dietary risks	418,350
High BMI	392,352
High LDL cholesterol	226,343
Impaired kidney function	214,740
Alcohol use	136,866
Non-optimal temperature	126,623
Drug use	104,141

Data from the US Burden of Disease Collaborators, 2021.

heart disease, unintentional injuries (including overdoses), and Alzheimer disease.

Many effective preventive services are underutilized, and few adults receive all of the most strongly recommended services. Several methods, including the use of provider or patient reminder systems (including interactive patient health records), reorganization of care environments, and possibly provision of financial incentives to clinicians (though this remains controversial), can increase utilization of preventive services, but such methods have not been widely adopted.

Ahmad FB et al. The leading causes of death in the US for 2020. JAMA. 2021;325:1829. [PMID: 33787821]
Levine DM et al. Quality and experience of outpatient care in the United States for adults with or without primary care. JAMA Intern Med. 2019;179:363. [PMID: 30688977]
US Burden of Disease Collaborators. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. JAMA. 2018;319:1444. [PMID: 29634829]
Woolf SH et al. Life expectancy and mortality rates in the United States, 1959–2017. JAMA. 2019;322:1996. [PMID: 31769830]

PREVENTION OF INFECTIOUS DISEASES

Much of the historic decline in the incidence and fatality rates of infectious diseases is attributable to public health measures—especially immunization, improved sanitation, nonpharmacologic interventions (eg, mask-wearing to prevent respiratory-transmissible conditions), and better nutrition. This observation has been reinforced by the experience during the global COVID-19 pandemic.

Immunization remains the best means of preventing many infectious diseases. Recommended immunization schedules for children and adolescents can be found online at http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html, and the schedule for adults is at http://www.cdc.gov/vaccines/schedules/hcp/adult.html (see also Chapter 30 and Chapter 32). In addition to the severe toll in morbidity and mortality from COVID-19, substantial morbidity and mortality continues to occur from vaccine-preventable diseases, such as hepatitis A, hepatitis B, influenza, and pneumococcal infections. The high incidence and mortality rates from COVID-19 and other recent outbreaks of vaccine-preventable diseases in the United States highlight the need to understand the association of vaccine hesistancy or refusal and disease epidemiology and methods for overcoming it.

The Advisory Committee on Immunization Practices recommendations for the following vaccines appears in Table 1–3: influenza; measles, mumps, and rubella; 23-valent pneumococcal polysaccharide vaccine; tetanus, diphtheria, and acellular pertussis; hepatitis B; and HPV.

Persons traveling to countries where infections are endemic should take the precautions described in Chapter 30 and at https://wwwnc.cdc.gov/travel/destinations/list. Immunization registries—confidential, population-based, computerized information systems that collect vaccination data about all residents of a geographic area—can be used to increase and sustain high vaccination coverage.

Globally, **COVID-19** has resulted in over 5 million deaths. COVID-19 is caused by SARS-CoV-2. The impact on frontline workers, including health care workers, has been substantial, and the pandemic has revealed profound inequities in health and health care. In the United States, the COVID-19 mortality rates are higher in Black, Latinx, and Native American people compared to White people. Three COVID-19 vaccines are currently approved or authorized in the United States (Pfizer-BioNTech/Comirnaty, Moderna, and Janssen [Johnson & Johnson]). Currently, the CDC recommends everyone ages 5 and older get a COVID-19 vaccine to help protect against COVID-19 (see Chapter 32). Recent guidance has recommended third-dose boosters to be administered 6 months after primary series completion for individuals receiving Pfizer and Moderna mRNA-vaccines and 2 months after those receiving the Janssen adenovirus vector vaccine.

The USPSTF recommends behavioral counseling for adolescents and adults who are sexually active and at increased risk for **sexually transmitted infections.** Sexually active women aged 24 years or younger and older women who are at increased risk for infection should be screened for chlamydia and gonorrhea. Screening HIV-positive men or men who have sex with men for syphilis every 3 months is associated with improved syphilis detection.

The CDC recommends universal HIV screening of all patients aged 13–64, and the USPSTF recommends that clinicians screen adolescents and adults aged 15–65 years. Clinicians should integrate biomedical and behavioral approaches for HIV prevention. In addition to reducing sexual transmission of HIV, initiation of antiretroviral therapy reduces the risk for AIDS-defining events and death among patients with less immunologically advanced disease.

Daily **preexposure prophylaxis (PrEP)** with the fixed-dose combination of tenofovir disoproxil 300 mg and emtricitabine 200 mg (Truvada) should be considered for people who are HIV-negative but at substantial risk for HIV infection. Studies of men who have sex with men suggest that PrEP is very effective in reducing the risk of

Table 1–3. Advisory Committee on Immunization Practices vaccine recommendations, 2021.

Vaccine	Recommendation	Comment
Influenza	Routine vaccination for all persons aged 6 months and older, including all adults An alternative high-dose inactivated vaccine is available for adults aged 65 years and older	When vaccine supply is limited, certain groups should be given priority, such as adults aged 50 years and older, individuals with chronic illness or immunosuppression, and pregnant women
MMR	Two doses for adults at high risk for exposure and transmission (eg, college students, health care workers); otherwise, one dose for adults aged 18 years and older	Physician documentation of disease is not acceptable evidence of MMR immunity
PPSV23	Adults aged 65 and older If PPSV23 was administered prior to age 65 years, administer one dose PPSV23 at least 5 years after previous dose A shared clinical decision-making approach is recommended for use of PCV13 in average-risk individuals aged 65 and older	
Tdap	Routine use of a single dose of for adults aged 19–64 years	Replaces the next booster dose of Td
Hepatitis B	Three-dose series is recommended for all children aged 0–18 years and high-risk individuals (ie, health care workers, injection drug users, people with ESKD) Recommended for diabetic patients aged 19–59 years Should be considered in diabetic persons age 60 and older	Prevents chronic hepatitis B and cirrhosis and their predispositions to HCC
HPV VLP	Routine HPV vaccination for children and adults aged 9–26 years Shared decision-making is recommended for some individuals between 27 and 45 years of age (vaccine is not licensed for adults older than 45 years)	Prevents persistent HPV infections effectively and thus may impact the rate of CIN II–II

CIN, cervical intraepithelial neoplasia; HCC, hepatocellular carcinoma; HPV VLP, human papillomavirus virus-like particle vaccine; MMR, measles, mumps, and rubella vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria toxoids vaccine; Tdap, tetanus, diphtheria, and five-component acellular pertussis vaccine.

contracting HIV. Patients taking PrEP should be encouraged to use other prevention strategies, such as consistent condom use to maximally reduce their risk. **Postexposure prophylaxis (PEP)** with combinations of antiretroviral drugs is widely used after occupational and nonoccupational contact and may reduce the risk of transmission by approximately 80%. PEP should be initiated within 72 hours of exposure.

Herpes zoster, caused by reactivation from previous varicella zoster virus infection, affects many older adults and people with immune system dysfunction. The ACIP recommends the herpes zoster subunit vaccine (HZ/su; Shingrix) be used for the prevention of herpes zoster and related complications in immunocompetent adults age 50 and older and in individuals who previously received Zostavax.

Centers for Disease Control and Prevention (CDC). COVID-19, 2021. https://www.cdc.gov/coronavirus/2019-ncov/index.html
Centers for Disease Control and Prevention (CDC). About COVID-19 vaccines (updated January 21, 2022). https://www.cdc.gov/coronavirus/2019-ncov/vaccines/about-vaccines/index.html
Centers for Disease Control and Prevention (CDC). Pneumococcal vaccination. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
Centers for Disease Control and Prevention (CDC). Recommended adult immunization schedule for ages 19 years or older, United States, 2020. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
Chou R et al. Epidemiology of and risk factors for coronavirus infection in health care workers: a living rapid review. Ann Intern Med. 2020;173:120. [PMID: 32369541]

PREVENTION OF CARDIOVASCULAR DISEASE

CVDs, including CHD and stroke, represent two of the most important causes of morbidity and mortality in developed countries. Several risk factors increase the risk for coronary disease and stroke. These risk factors can be divided into those that are modifiable (eg, lipid disorders, hypertension, cigarette smoking) and those that are not (eg, age, sex, family history of early coronary disease). Impressive declines in age-specific mortality rates from heart disease and stroke have been achieved in all age groups in North America from 1980 to 2015, in large part through improvement of modifiable risk factors: reductions in cigarette smoking, improvements in lipid levels, and more aggressive detection and treatment of hypertension. However, the past several years have seen a disturbing increase in cardiovascular deaths in the United States and leveling off of the reduction in cardiovascular mortality rates. This section considers the role of screening for cardiovascular risk and the use of effective therapies to reduce such risk. Key recommendations for cardiovascular prevention are shown in Table 1–4. Guidelines encourage regular assessment of global cardiovascular risk in adults 40–79 years of age without known CVD, using standard

Table 1–4. Expert recommendations for cardiovascular risk prevention methods: USPSTF.[1]

Prevention Method	Recommendation/[Year Issued]
Screening for AAA	Recommends one-time screening for AAA by ultrasonography in men aged 65–75 years who have ever smoked. (B) Selectively offer screening for AAA in men aged 65–75 years who have never smoked. (C) Current evidence is insufficient to assess the balance of benefits and harms of screening for AAA in women aged 65–75 years who have ever smoked or have a family history of AAA. (I) Recommends against routine screening for AAA in women who have never smoked and have no family history of AAA. (D) [2019]
Aspirin use	Recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50–59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B) The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60–69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C) The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years or older than age 70. (I) [2016]
Blood pressure screening	Recommends screening for hypertension in adults 18 years or older with office blood pressure measurement. Recommends obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment. (A) [2021]
Serum lipid screening and use of statins for prevention	Recommends that adults without a history of CVD use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: (1) they are aged 40–75 years; (2) they have one or more CVD risk factors (ie, dyslipidemia, diabetes mellitus, hypertension, or smoking); and (3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40–75 years. See the "Clinical Considerations" section of the USPSTF recommendations[1] for more information on lipids screening and the assessment of cardiovascular risk. (B) Concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults aged 76 years and older without a history of heart attack or stroke. (I) [2016]
Counseling about healthful diet and physical activity for CVD prevention	Recommends offering or referring adults with cardiovascular disease risk factors to behavioral counseling interventions to promote a healthy diet and physical activity. (B) [2020] Recommends that primary care professionals individualize the decision to offer or refer adults without obesity who do not have hypertension, dyslipidemia, abnormal blood glucose levels, or diabetes to behavioral counseling to promote a healthful diet and physical activity. (C) [2017]
Screening for diabetes mellitus	The USPSTF recommends screening for prediabetes and type 2 diabetes in adults aged 35–70 years who have overweight or obesity. Clinicians should offer or refer patients with prediabetes to effective preventive interventions. (B) [2021]
Screening for smoking and counseling to promote cessation	Recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide those who use tobacco behavioral interventions, and prescribe US FDA–approved pharmacotherapy to nonpregnant adults. (A) [2021]

USPSTF recommendations available at http://www.uspreventiveservicestaskforce.org/BrowseRec/Index/browse-recommendations.
Recommendation A: The USPSTF strongly recommends that clinicians routinely provide the service to eligible patients. (The USPSTF found good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.)
Recommendation B: The USPSTF recommends that clinicians routinely provide the service to eligible patients. (The USPSTF found at least fair evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.)
Recommendation C: The USPSTF makes no recommendation for or against routine provision of the service.
Recommendation D: The USPSTF recommends against routinely providing the service to asymptomatic patients. (The USPSTF found at least fair evidence that the service is ineffective or that harms outweigh benefits.)
Recommendation I: The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing the service.

cardiovascular risk factors. The role of nontraditional risk factors for improving risk estimation remains unclear.

Cho L et al. Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75:2602. [PMID: 32439010]
Roth GA et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76:2982. [PMID: 33309175]

Abdominal Aortic Aneurysm

One-time screening for AAA by ultrasonography is recommended by the USPSTF (B recommendation) in men aged 65–75 years who have ever smoked. One-time screening for AAA is associated with a relative reduction in odds of AAA-related mortality over 12–15 years (OR, 0.65 [95% CI 0.57–0.74]) and a similar reduction in AAA-related ruptures (OR, 0.62 [95% CI 0.55–0.70]). Women who have never smoked and who have no family history of AAA do not appear to benefit from such screening (D recommendation); the current evidence for women who have ever smoked or who have a family history of AAA is insufficient to assess the balance of risks versus benefits (I recommendation) (Table 1–4).

Guirguis-Blake JM et al. Primary care screening for abdominal aortic aneurysm: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2019;322:2219. [PMID: 31821436]
US Preventive Services Task Force, Owens DK et al. Screening for abdominal aortic aneurysm: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;322:2211. [PMID: 31821437]
Ying AJ et al. Abdominal aortic aneurysm screening: a systematic review and meta-analysis of efficacy and cost. Ann Vasc Surg. 2019;54:298. [PMID: 30081169]

Cigarette Smoking

Cigarette smoking remains the most important cause of preventable morbidity and early mortality. In 2019, there were an estimated 7.69 million deaths in the world attributable to smoking and tobacco use (13.6% of all deaths worldwide); smoking is the second leading cause of disability-adjusted life-years lost overall and leading cause among men. Cigarettes are responsible for one in every five deaths in the United States, or over 480,000 deaths annually. Annual cost of smoking-related health care is approximately $130 billion in the United States, with another $150 billion in productivity losses. Fortunately, US smoking rates have been declining; in 2015, 15.1% of US adults were smokers, and by 2018, 13.7% were smokers. Global direct health care costs from smoking in 2012 were estimated at $422 billion, with total costs of over $1.4 trillion.

Over 1.3 million deaths worldwide are attributed to secondhand smoke in 2019.

Although tobacco use constitutes one of the most serious common medical problems, it is undertreated. Almost 40% of smokers attempt to quit each year, but only 4% are successful. Persons whose clinicians advise them to quit are 1.6 times as likely to attempt quitting. Over 70% of smokers see a physician each year, but only 20% of them receive any medical quitting advice or assistance.

Factors associated with successful cessation include having a rule against smoking in the home, being older, and having greater education. Several effective clinical interventions are available to promote smoking cessation, including counseling, pharmacotherapy, and combinations of the two.

Helpful counseling strategies are shown in Table 1–5. Additionally, a system should be implemented to identify smokers, and advice to quit should be tailored to the patient's level of readiness to change. All patients trying to quit should be offered pharmacotherapy (Table 1–6) except those with medical contraindications, women who are

Table 1–5. Inquiries to help in support of smoking cessation.

Component	Helpful Clinician Statements and Inquiries
Communicate your caring and concern	"I am concerned about the effects of smoking on your health… • and want you to know that I am willing to help you quit." • and so how do you feel about quitting?" • do you have any fears or ambivalent feelings about quitting?"
Encourage the patient to talk about the quitting process	"Tell me… • why do you want to quit smoking?" • when you tried quitting smoking in the past, what sort of difficulties did you encounter?" • were you able to succeed at all, even for a while?" • what concerns or worries do you have about quitting now?"
Provide basic information about smoking (eg, its addictive nature) and successful quitting (eg, nature and time course of withdrawal)	"Did you know that… • the nicotine in cigarette smoke is highly addictive?" • within a day of stopping, you will notice nicotine withdrawal symptoms, such as irritability and craving?" • after you quit, any smoking (even a single puff) makes it likely that you will fully relapse into smoking again?"
Encourage the patient to make a quit attempt	"I want you to reassure you that… • as your clinician, I believe you are going to be able to quit." • there are now available many effective smoking cessation treatments." • more than half the people who have *ever* smoked have now successfully quit."

Table 1–6. Medications for tobacco dependence and smoking cessation.

Drug	Some Formulations	Usual Adult Dosage[1,2]	Cost 30/days
Nicotine Replacement Therapies (NRTs)			
Nicotine transdermal patch[3] – generic (NicoDerm CQ)	7, 14, 21 mg/24-h patches	1 patch/day[4]	$51.40
Nicotine polacrilex gum[3] – generic (Nicorette gum)	2, 4 mg/pieces	8–24 pieces/day[4,5,6]	$63.12
Nicotine polacrilex lozenge[3,7] – generic (Nicorette lozenge)	2, 4 mg/lozenges	8–20 lozenges/day[4,5,8]	$66.24
Nicotine oral inhaler – Nicotrol	10 mg cartridges[9]	4–16 cartridges/day[4]	$578.66
Nicotine nasal spray – Nicotrol NS	200 sprays/10 mL bottles (0.5 mg/spray)	2 sprays 8–40×/day (max 10 sprays/h)[3]	$607.60 (4-bottle package)
Dopaminergic-Noradrenergic Reuptake Inhibitor			
Bupropion SR – generic	100, 150, 200 mg SR tablets[10]	150 mg orally once daily × 3 days, then 150 mg orally twice daily	$112.80
Nicotinic Receptor Partial Agonist			
Varenicline tartrate – Chantix	0.5, 1 mg tablets	0.5 mg orally once daily × 3 days, then 0.5 mg twice daily on days 4–7, then 1 mg twice daily	$603.41

SR, sustained-release.
[1]Dosage reductions may be needed for liver or kidney impairment.
[2]Patients should receive a minimum of 3–6 months of effective therapy. In general, the dosage of NRTs can be tapered at the end of treatment; bupropion SR and varenicline can usually be stopped without a gradual dosage reduction, but some clinicians recommend a taper.
[3]Available over the counter for persons ≥ 18 years old.
[4]See expanded table for dosage titration instructions, available at: medicalletter.org/TML-article-1576c.
[5]Avoid eating or drinking within 15 minutes of using a gum or lozenge.
[6]A second piece of gum can be used within 1 hour. Continuously chewing one piece after another is not recommended.
[7]Also available in a mini-lozenge.
[8]Maximum of 5 lozenges in 6 hours or 20 lozenges/day. Use of more than 1 lozenge at a time or continuously using one after another is not recommended.
[9]Each cartridge delivers 4 mg of nicotine.
[10]Only the generic 150-mg SR tablets are FDA-approved as a smoking cessation aid.
Reprinted with special permission from The Medical Letter on Drugs and Therapeutics, July 15, 2019; Vol. 61 (1576):106.
Average wholesale price (AWP, for AB-rated generic when available) for quantity listed. Source: IBM Micromedex® Red Book (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at https://www-micromedexsolutions-com.proxy.hsl.ucdenver.edu (cited: March, 11, 2022). AWP may not accurately represent the actual pharmacy cost because wide contractual variations exist among institutions.

pregnant or breast-feeding, and adolescents. Weight gain occurs in most patients (80%) following smoking cessation. Average weight gain is 2 kg, but for some (10–15%), major weight gain—over 13 kg—may occur. Planning for the possibility of weight gain, and means of mitigating it, may help with maintenance of cessation.

Several pharmacologic therapies shown to be effective in promoting cessation are summarized in Table 1–6. Nicotine replacement therapy doubles the chance of successful quitting. The nicotine patch, gum, and lozenges are available over the counter and nicotine nasal spray and inhalers by prescription. The sustained-release antidepressant drug bupropion (150–300 mg/day orally) is an effective smoking cessation agent and is associated with minimal weight gain, although seizures are a contraindication. It acts by boosting brain levels of dopamine and norepinephrine, mimicking the effect of nicotine. Varenicline, a partial nicotinic acetylcholine-receptor agonist, has been shown to improve cessation rates; however, its adverse effects, particularly its effects on mood, are not completely understood and warrant careful consideration. No single pharmacotherapy is clearly more effective than others, so patient preferences and data on adverse effects should be taken into account in selecting a treatment. Combination therapy is more effective than a single pharmacologic modality. The efficacy of e-cigarettes in smoking cessation has not been well evaluated, and some users may find them addictive. Recent reports of "vaping-related" lung disease should prompt additional caution in the use of unregulated nicotine delivery devices for smoking cessation (see Chapter 9).

Clinicians should not show disapproval of patients who fail to stop smoking or who are not ready to make a quit attempt. Thoughtful advice that emphasizes the benefits of cessation and recognizes common barriers to success can

increase motivation to quit and quit rates. An upcoming medical procedure or intercurrent illness or hospitalization may motivate even the most addicted smoker to quit.

Individualized or group counseling is very cost effective, even more so than treating hypertension. Smoking cessation counseling by telephone ("quitlines") and text messaging–based interventions have both proved effective. An additional strategy is to recommend that any smoking take place outdoors to limit the effects of passive smoke on housemates and coworkers. This can lead to smoking reduction and quitting.

Public policies, including higher cigarette taxes and more restrictive public smoking laws, have also been shown to encourage cessation, as have financial incentives directed to patients.

Anonymous. Drugs for smoking cessation. Med Lett Drugs Ther. 2019;61:105. [PMID: 31381546]
Black N et al. Behaviour change techniques associated with smoking cessation in intervention and comparator groups of randomized controlled trials: a systematic review and meta-regression. Addiction. 2020;115:2008. [PMID: 32196796]
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Hollands GJ et al. Interventions to increase adherence to medications for tobacco dependence. Cochrane Database Syst Rev. 2019;8:CD009164. [PMID: 31425618]
Tibuakuu M et al. National trends in cessation counseling, prescription medication use, and associated costs among US adult cigarette smokers. JAMA Netw Open. 2019;2:e194585. [PMID: 31125108]
Villanti AC et al. Smoking-cessation interventions for U.S. young adults: updated systematic review. Am J Prev Med. 2020;59:123. [PMID: 32418800]

Lipid Disorders

Higher LDL cholesterol concentrations and lower HDL levels are associated with an increased risk of CHD (see Chapter 28). Measurement of total and HDL cholesterol levels can help assess the degree of CHD risk. The best age to start screening is controversial, as is its frequency. Cholesterol-lowering therapy reduces the relative risk of CHD events, with the degree of reduction proportional to the reduction in LDL cholesterol achieved, at least at initial LDL levels greater than 100 mg/dL. The absolute benefits of screening for—and treating—abnormal lipid levels depend on the presence and level of other cardiovascular risk factors, including hypertension, diabetes mellitus, smoking, age, and sex. If other risk factors are present, atherosclerotic CVD risk is higher and the potential benefits of therapy are greater. Patients with known CVD are at higher risk and have larger benefits from reduction in LDL cholesterol. The optimal risk threshold for initiating statins for primary prevention remains somewhat controversial, although most guidelines now suggest statin therapy when the 10-year atherosclerotic cardiovascular risk is greater than 10%. Use of a cardiovascular risk calculator can help inform decision making for primary prevention.

Evidence for the effectiveness of statin-type drugs is better than for the other classes of lipid-lowering agents or dietary changes specifically for improving lipid levels. Multiple large, randomized, placebo-controlled trials have demonstrated important reductions in total mortality, major coronary events, and strokes with lowering levels of LDL cholesterol by statin therapy for patients with known CVD. Statins also reduce cardiovascular events for patients with diabetes mellitus. For patients with no previous history of cardiovascular events or diabetes, meta-analyses have shown important reductions of cardiovascular events.

Newer antilipidemic monoclonal antibody agents (eg, evolocumab and alirocumab) lower LDL cholesterol by 50–60% by binding proprotein convertase subtilisin kexin type 9 (PCSK9), which decreases the degradation of LDL receptors. PCSK9 inhibitors also decrease Lp(a) levels. These newer agents are very expensive so are often used mainly in high-risk patients when statin therapy does not reduce the LDL cholesterol sufficiently at maximally tolerated doses or when patients are intolerant of statins. So far, few side effects have been reported with PCSK9 inhibitor use.

Guidelines for statin and PCSK9 therapy are discussed in Chapter 28.

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Mortensen MB et al. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort. Lancet. 2020;396:1644. [PMID: 33186534]
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Hypertension

According to the American Heart Association, over 133 million US adults have hypertension, of which approximately 83 million are eligible for pharmacologic treatment. Of these 83 million, hypertension is treated in only about 66% and well controlled in only about 30% (see Chapter 11). In every adult age group, higher values of systolic and diastolic blood pressure carry greater risks of stroke and heart failure. Systolic blood pressure is a better predictor of morbid events than diastolic blood pressure. Home monitoring is better correlated with target organ damage than clinic-based values. Clinicians can apply specific blood pressure criteria, such as those of the Joint National Committee or American Heart Association guidelines, along with consideration of the patient's cardiovascular risk and personal values, to decide at what levels treatment should be considered in individual cases.

Primary prevention of hypertension can be accomplished by strategies aimed at both the general population and special high-risk populations. The latter include persons with high-normal blood pressure or a family history of hypertension, Blacks, and individuals with various behavioral risk factors, such as physical inactivity; excessive consumption of salt, alcohol, or calories; and deficient

intake of potassium. Effective interventions for primary prevention of hypertension include reduced sodium and alcohol consumption, weight loss, and regular exercise. Potassium supplementation lowers blood pressure modestly, and a diet high in fresh fruits and vegetables and low in fat, red meats, and sugar-containing beverages also reduces blood pressure. Interventions of unproven efficacy include pill supplementation of potassium, calcium, magnesium, fish oil, or fiber; macronutrient alteration; and stress management.

Improved identification and treatment of hypertension has been a major cause of the decline in stroke deaths as well as the reduction in incidence of heart failure–related hospitalizations; more recently, stalled progress in control of hypertension has led to slowing of improvements in cardiovascular outcomes. Because hypertension is usually asymptomatic, screening is strongly recommended to identify patients for treatment. Elevated office readings should be confirmed with repeated measurements, ideally from ambulatory monitoring or home measurements. Despite strong recommendations in favor of screening and treatment, hypertension control remains suboptimal. An intervention that included both patient and provider education was more effective than provider education alone in achieving control of hypertension, suggesting the benefits of patient participation; another trial found that home monitoring combined with telephone-based nurse support was more effective than home monitoring alone for blood pressure control. Pharmacologic management of hypertension is discussed in Chapter 11.

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Chemoprevention

Regular use of low-dose aspirin (81–325 mg) can reduce cardiovascular events but increases GI bleeding and hemorrhagic stroke. The potential benefits of aspirin may exceed the possible adverse effects among middle-aged adults who are at increased cardiovascular risk, which can be defined as a 10-year risk of greater than 10%, and who do not have an increased risk of bleeding. A newer trial in older healthy adults did not find clear benefit from aspirin for reduction of cardiovascular events and saw an increase in all-cause mortality with aspirin. Therefore, aspirin should not be routinely initiated in healthy adults over age 70.

NSAIDs may reduce the incidence of colorectal adenomas and polyps but may also increase heart disease and GI bleeding, and thus are not recommended for colon cancer prevention in average-risk patients.

Antioxidant vitamin (vitamin E, vitamin C, and beta-carotene) supplementation produced no significant reductions in the 5-year incidence of—or mortality from—vascular disease, cancer, or other major outcomes in high-risk individuals with CAD, other occlusive arterial disease, or diabetes mellitus.

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PREVENTION OF OSTEOPOROSIS

See Chapter 26.

Osteoporosis, characterized by low bone mineral density, is common and associated with an increased risk of fracture. The lifetime risk of an osteoporotic fracture is approximately 50% for women and 30% for men. Osteoporotic fractures can cause significant pain and disability. As such, research has focused on means of preventing osteoporosis and related fractures. Primary prevention strategies include calcium supplementation, vitamin D supplementation, and exercise programs. The effectiveness of calcium and vitamin D for fracture prevention remains controversial, particularly in noninstitutionalized individuals.

Screening for osteoporosis on the basis of low bone mineral density is recommended for women over age 65, based on indirect evidence that screening can identify women with low bone mineral density and that treatment of women with low bone density with bisphosphonates is effective in reducing fractures. However, real-world adherence to pharmacologic therapy for osteoporosis is low: one-third to one-half of patients do not take their medication as directed. Screening for osteoporosis is also recommended in younger women who are at increased risk. The effectiveness of screening in men has not been established. Concern has been raised that bisphosphonates may increase the risk of certain uncommon atypical types of femoral fractures and rare osteonecrosis of the jaw, making consideration of the benefits and risks of therapy important when considering osteoporosis screening.

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PREVENTION OF PHYSICAL INACTIVITY

Lack of sufficient physical activity is the second most important contributor to preventable deaths, trailing only tobacco use. The US Department of Health and Human Services and the CDC recommend that adults (including older adults) engage in 150 minutes of moderate-intensity (such as brisk walking) or 75 minutes of vigorous-intensity (such as jogging or running) aerobic activity or an equivalent mix of moderate- and vigorous-intensity aerobic activity each week. In addition to activity recommendations, the CDC recommends activities to strengthen all major muscle groups (abdomen, arms, back, chest, hips, legs, and shoulders) at least twice a week.

Patients who engage in regular moderate to vigorous exercise have a lower risk of MI, stroke, hypertension, hyperlipidemia, type 2 diabetes mellitus, diverticular disease, and osteoporosis. Regular exercise may also have a positive effect on executive function in older adults.

In longitudinal cohort studies, individuals who report higher levels of leisure-time physical activity are less likely to gain weight. Conversely, individuals who are overweight are less likely to stay active. However, at least 60 minutes of daily moderate-intensity physical activity may be necessary to maximize weight loss and prevent significant weight regain. Moreover, adequate levels of physical activity appear to be important for the prevention of weight gain and the development of obesity.

Physical activity can be incorporated into any person's daily routine. The basic message should be the more the better, and anything is better than nothing.

When counseling patients, clinicians should advise patients about both the benefits and risks of exercise, prescribe an exercise program appropriate for each patient, and provide advice to help prevent injuries and cardiovascular complications.

Although primary care providers regularly ask patients about physical activity and advise them with verbal counseling, few providers provide written prescriptions or perform fitness assessments. Tailored interventions may potentially help increase physical activity in individuals. Exercise counseling with a prescription, eg, for walking at either a hard intensity or a moderate intensity with a high frequency, can produce significant long-term improvements in cardiorespiratory fitness. To be effective, exercise prescriptions must include recommendations on type, frequency, intensity, time, and progression of exercise and must follow disease-specific guidelines. Several factors influence physical activity behavior, including personal, social (eg, family and work), and environmental (eg, access to exercise facilities and well-lit parks) factors.

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PREVENTION OF OVERWEIGHT & OBESITY

Obesity is now a true epidemic and public health crisis that both clinicians and patients must face. Normal body weight is defined as a BMI of less than 25, overweight is defined as a BMI of 25.0–29.9, and obesity as a BMI greater than 30.

Risk assessment of the overweight and obese patient begins with determination of BMI, waist circumference for those with a BMI of 35 or less, presence of comorbid conditions, and a fasting blood glucose and lipid panel. Obesity is clearly associated with type 2 diabetes mellitus, hypertension, hyperlipidemia, cancer, osteoarthritis, cardiovascular disease, obstructive sleep apnea, and asthma.

Obesity is associated with a higher all-cause mortality rate. Data suggest an increase among those with grades 2 and 3 obesity (BMI more than 35); however, the impact on all-cause mortality among overweight (BMI 25–30) and grade 1 obesity (BMI 30–35) is questionable. Persons with a BMI of 40 or higher have death rates from cancers that are 52% higher for men and 62% higher for women than the rates in men and women of normal weight.

Prevention of overweight and obesity involves both increasing physical activity and dietary modification to reduce caloric intake. Adequate levels of physical activity appear to be important for the prevention of weight gain and the development of obesity. Physical activity programs consistent with public health recommendations may promote modest weight loss (~2 kg); however, the amount of weight loss for any one individual is highly variable.

Clinicians can help guide patients to develop personalized eating plans to reduce energy intake, particularly by recognizing the contributions of fat, concentrated carbohydrates, and large portion sizes (see Chapter 29). Patients typically underestimate caloric content, especially when consuming food away from home. Providing patients with caloric and nutritional information may help address the current obesity epidemic.

Commercial weight loss programs are effective in promoting weight loss and weight loss management. A randomized controlled trial of over 400 overweight or obese women demonstrated the effectiveness of a free prepared meal and incentivized structured weight loss program compared with usual care.

Weight loss strategies using dietary, physical activity, or behavioral interventions can produce significant improvements in weight among persons with prediabetes and a significant decrease in diabetes incidence. Lifestyle interventions including diet combined with physical activity are effective in achieving weight loss and reducing cardiometabolic risk factors among patients with severe obesity.

Bariatric surgical procedures, eg, adjustable gastric band, sleeve gastrectomy, and Roux-en-Y gastric bypass, are reserved for patients with morbid obesity whose BMI exceeds 40, or for less severely obese patients (with BMIs between 35 and 40) with high-risk comorbid conditions such as life-threatening cardiopulmonary problems or severe diabetes mellitus. In selected patients, surgery can produce substantial weight loss (10–159 kg) over 1–5 years, with rare but sometimes severe complications. Nutritional deficiencies are one complication of bariatric surgical procedures and close monitoring of a patient's metabolic and nutritional status is essential.

Finally, clinicians seem to share a general perception that almost no one succeeds in long-term maintenance of weight loss. However, research demonstrates that approximately 20% of overweight individuals are successful at long-term weight loss (defined as losing 10% or more of initial body weight and maintaining the loss for 1 year or longer).

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CANCER PREVENTION

Primary Prevention

Persons who engage in regular physical exercise and avoid obesity have lower rates of breast and colon cancer. Chemoprevention has been widely studied for primary cancer prevention without clear evidence of benefits (see earlier Chemoprevention section and Chapter 39). Use of tamoxifen, raloxifene, and aromatase inhibitors for breast cancer prevention is discussed in Chapters 17 and 39. Hepatitis B vaccination can prevent HCC. Screening and treatment of hepatitis C is another strategy to prevent HCC (see Chapter 16); new recommendations have extended the population eligible for screening. HPV virus-like particle (VLP) vaccine is recommended to prevent cervical cancer (Table 1–3). HPV vaccines may also have a role in the prevention of HPV-related head and neck and possibly anal cancers. The USPSTF recommends genetic counseling and, if indicated after counseling, genetic testing for women whose family or personal history is associated with an increased risk of harmful mutations in the *BRCA 1/2* gene. Guidelines for optimal cancer screening in adults over the age of 75 are unsettled; thus, an individualized approach that considers differences in disease risk rather than chronological age alone is recommended.

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US Preventive Services Task Force; Owens DK et al. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019;322:652. [PMID: 31429903]

Screening & Early Detection

Screening prevents death from cancers of the breast, colon, and cervix. Current cancer screening recommendations from the USPSTF are available online at https://www.uspreventiveservicestaskforce.org/BrowseRec/Index/browse-recommendations. Despite an increase in rates of screening for breast, cervical, and colon cancer over the last decade, overall screening for these cancers is suboptimal.

Though breast cancer mortality is reduced with mammography screening, screening mammography has both benefits and downsides. Clinicians should discuss the risks and benefits with each patient and consider individual patient preferences when deciding when to begin screening (see Chapters 17 and e6).

Screening for testicular cancers among asymptomatic adolescent or adult males is not recommended by the USPSTF. Prostate cancer screening remains controversial, since no completed trials have answered the question of whether early detection and treatment after screen detection produce sufficient benefits to outweigh harms of treatment. For men between the ages of 55 and 69, the decision to screen should be individualized and include a discussion of its risks and benefits with a clinician. The USPSTF recommends against PSA-based prostate cancer screening for men older than age 70 years (grade D recommendation).

The USPSTF recommends colorectal cancer screening for adults aged 45–75 years and selectively screening adults aged 76–85 years (considering the patient's overall health, prior screening history, and patient's preferences).

Annual or biennial fecal occult blood testing reduces mortality from colorectal cancer. Fecal immunochemical tests (FIT) are superior to guaiac-based fecal occult blood tests (gFOBT) in detecting advanced adenomatous polyps and colorectal cancer, and patients are more likely to favor FIT over gFOBT. CT colonography (virtual colonoscopy) is a noninvasive option in screening for colorectal cancer. It has been shown to have a high safety profile and performance similar to colonoscopy.

The USPSTF recommends screening for cervical cancer in women aged 21–65 years with a Papanicolaou smear (cytology) every 3 years or, for women aged 30–65 years who desire longer intervals, screening with cytology and HPV testing every 5 years. The American Cancer Society recommends screening for people aged 25–65 years with primary HPV testing every 5 years. The USPSTF recommends against screening in women younger than 21 years of age and average-risk women over 65 with adequate negative prior screenings. Receipt of HPV vaccination has no impact on screening intervals.

Women whose cervical specimen HPV tests are positive but cytology results are otherwise negative should repeat co-testing in 12 months (option 1) or undergo HPV-genotype–specific testing for types 16 or 16/18 (option 2). Colposcopy is recommended in women who test positive

for types 16 or 16/18. Women with atypical squamous cells of undetermined significance (ASCUS) on cytology and a negative HPV test result should continue routine screening as per age-specific guidelines.

The USPSTF recommends offering annual lung cancer screening with low-dose CT to current smokers aged 50 to 80 years and 20-pack-year smoking history or to smokers who quit within the past 15 years. Screening should stop once a person has not smoked for 15 years or a health problem that significantly limits life expectancy has developed. Screening should not be viewed as an alternative to smoking cessation but rather as a complementary approach.

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US Preventive Services Task Force; Grossman DC et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:1901. [PMID: 29801017]
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PREVENTION OF INJURIES & VIOLENCE

Injuries remain the most important cause of loss of potential years of life before age 65. Homicide and motor vehicle accidents are a major cause of injury-related deaths among young adults, and accidental falls are the most common cause of injury-related death in older adults. Approximately one-third of all injury deaths include a diagnosis of traumatic brain injury, which has been associated with an increased risk of suicide. Although motor vehicle accident deaths per miles driven have declined in the United States, there has been an increase in motor vehicle accidents related to distracted driving (using a cell phone, texting, eating).

Men ages 16–35 are at especially high risk for serious injury and death from accidents and violence, with Black and Latino men at greatest risk. Deaths from firearms have reached epidemic levels in the United States. Having a gun in the home increases the likelihood of homicide nearly threefold and of suicide fivefold. Educating clinicians to recognize and treat depression as well as restricting access to lethal methods have been found to reduce suicide rates.

Clinicians have a critical role in the detection, prevention, and management of intimate partner violence (see Chapter e6). The USPSTF recommends screening women of childbearing age for intimate partner violence and providing or referring women to intervention services when needed. Inclusion of a single question in the medical history—"At any time, has a partner ever hit you, kicked you, or otherwise physically hurt you?"—can increase identification of this common problem. Assessment for abuse and offering of referrals to community resources create the potential to interrupt and prevent recurrence of domestic violence and associated trauma. Clinicians should take an active role in following up with patients whenever possible, since intimate partner violence screening with passive referrals to services may not be adequate.

Physical and psychological abuse, exploitation, and neglect of older adults are serious, underrecognized problems; they may occur in up to 10% of elders. Risk factors for elder abuse include a culture of violence in the family; a demented, debilitated, or depressed and socially isolated victim; and a perpetrator profile of mental illness, alcohol or drug abuse, or emotional and/or financial dependence on the victim. Clues to elder mistreatment include the patient's ill-kempt appearance, recurrent urgent-care visits, missed appointments, suspicious physical findings, and implausible explanations for injuries.

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Kirk L et al. What barriers prevent health professionals screening women for domestic abuse? A literature review. Br J Nurs. 2020;29:754. [PMID: 32649247]
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PREVENTION OF SUBSTANCE USE DISORDER: ALCOHOL & ILLICIT DRUGS

Unhealthy alcohol use is a major public health problem in the United States, where approximately 51% of adults 18 years and older are current regular drinkers (at least 12 drinks in the past year). The spectrum of alcohol use disorders includes alcohol dependence, harmful pattern use of alcohol, and entities such as alcohol intoxication, alcohol withdrawal, and several alcohol-induced mental disorders. The ICD-11 includes a new category: hazardous alcohol use. Categorized as a risk factor, hazardous alcohol use is a pattern of alcohol use that appreciably increases the risk of physical or mental health harmful consequences to the user.

Underdiagnosis and undertreatment of alcohol misuse is substantial, both because of patient denial and lack of detection of clinical clues.

As with cigarette use, clinician identification and counseling about unhealthy alcohol use are essential. The USPSTF recommends screening adults aged 18 years and older for unhealthy alcohol use. The National Institute on Alcohol Abuse and Alcoholism recommends the following single-question screening test (validated in primary care settings): "How many times in the past year have you had X or more drinks in a day?" (X is 5 for men and 4 for women, and a response of more than 1 time is considered positive.)

Those who screen positive on the single-item questionnaire should complete the Alcohol Use Disorder

Identification Test (AUDIT), which consists of questions on the quantity and frequency of alcohol consumption, on alcohol dependence symptoms, and on alcohol-related problems (Table 1–7).

Clinicians should provide those who screen positive for hazardous or risky drinking with brief behavioral counseling interventions to reduce alcohol misuse. Use of screening procedures and brief intervention methods (see Chapter 25) can produce a 10–30% reduction in long-term alcohol use and alcohol-related problems. Those whose AUDIT scores suggest alcohol use disorder (AUDIT > 12) should undergo more extensive evaluation and potential referral for treatment.

Deaths due to opioid overdose have dramatically increased. Opioid risk mitigation strategies include use of risk assessment tools, treatment agreements (contracts), and urine drug testing. Additional strategies include establishing and strengthening prescription drug monitoring programs, regulating pain management facilities, and establishing dosage thresholds requiring consultation with pain specialists. Medication-assisted treatment, the use of medications with counseling and behavioral therapy, is effective in the prevention of opioid overdose and substance abuse disorders. Methadone, buprenorphine, and naltrexone are FDA approved for use in medication-assisted treatment. Buprenorphine has potential as a medication to ameliorate the symptoms and signs of withdrawal from opioids and is effective in reducing concomitant cocaine and opioid abuse. The FDA supports greater access to naloxone and is currently exploring options to make naloxone more available to treat opioid overdose. (See Chapter 5.)

Use of illegal drugs—including cocaine, methamphetamine, and so-called designer drugs—either sporadically or episodically remains an important problem. Lifetime prevalence of drug abuse is approximately 8% and is generally greater among men, young and unmarried individuals, Native Americans, and those of lower socioeconomic status. As with alcohol, drug abuse disorders often coexist with personality disorders, anxiety disorders, and other substance abuse disorders.

Clinical aspects of substance abuse are discussed in Chapter 25.

Chou R et al. Interventions for unhealthy drug use—supplemental report: a systematic review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020 Jun. Report No.: 19-05255-EF-2. https://www.ncbi.nlm.nih.gov/books/NBK558205/ [PMID: 32550674]

Table 1–7. Screening for alcohol abuse using the Alcohol Use Disorder Identification Test (AUDIT).

(Scores for response categories are given in parentheses. Added together, Total Scores range from 0 to 40, with scores of 1 to 7 suggesting low-risk drinking; 8 to 14, hazardous or harmful drinking; and >15, alcohol dependence.)				
1. How often do you have a drink containing alcohol?				
(0) Never	(1) Monthly or less	(2) Two to four times a month	(3) Two or three times a week	(4) Four or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?				
(0) 1 or 2	(1) 3 or 4	(2) 5 or 6	(3) 7 to 9	(4) 10 or more
3. How often do you have six or more drinks on one occasion?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
4. How often during the past year have you found that you were not able to stop drinking once you had started?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
5. How often during the past year have you failed to do what was normally expected of you because of drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
6. How often during the past year have you needed a first drink in the morning to get yourself going after a heavy drinking session?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
7. How often during the past year have you had a feeling of guilt or remorse after drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
8. How often during the past year have you been unable to remember what happened the night before because you had been drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost daily
9. Have you or has someone else been injured as a result of your drinking?				
(0) No		(2) Yes, but not in the past year		(4) Yes, during the past year
10. Has a relative or friend or a doctor or other health worker been concerned about your drinking or suggested you cut down?				
(0) No		(2) Yes, but not in the past year		(4) Yes, during the past year

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Common Symptoms

2

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COUGH

ESSENTIAL INQUIRIES

- Age, occupational history, environmental exposures, risk of infection with SARS-CoV-2, and duration of cough.
- Use of tobacco, cannabis, e-cigarettes (vaping).
- Dyspnea (at rest or with exertion).
- Vital signs (heart rate, respiratory rate, body temperature); pulse oximetry.
- Chest examination.
- Chest radiography, especially when unexplained cough lasts > 3–6 weeks.

General Considerations

Cough is the most common symptom for which patients seek medical attention. Cough results from stimulation of mechanical or chemical afferent nerve receptors in the bronchial tree. Effective cough depends on an intact afferent–efferent reflex arc, adequate expiratory and chest wall muscle strength, and normal mucociliary production and clearance.

Clinical Findings

A. Symptoms

Distinguishing **acute** (less than 3 weeks), **persistent** (3–8 weeks), and **chronic** (more than 8 weeks) cough illness syndromes is a useful first step in evaluation. Postinfectious cough lasting 3–8 weeks has also been referred to as **subacute** cough to distinguish this common, distinct clinical entity from acute and chronic cough.

1. Acute cough—In healthy adults, most acute cough syndromes are due to viral respiratory tract infections. Additional features of infection such as fever, nasal congestion, and sore throat help confirm this diagnosis. Dyspnea (at rest or with exertion) may reflect a more serious condition, and further evaluation should include assessment of oxygenation (pulse oximetry or arterial blood gas measurement), airflow (peak flow or spirometry), and pulmonary parenchymal disease (chest radiography). The timing and character of the cough are not very useful in establishing the cause of acute cough syndromes, although cough-variant asthma should be considered in adults with prominent nocturnal cough, and persistent cough with phlegm increases the likelihood of COPD. The presence of posttussive emesis or inspiratory whoop in adults modestly increases the likelihood of pertussis, and the absence of paroxysmal cough and the presence of fever decrease its likelihood. Loss of smell or taste accompanying a new cough illness is specific but not sensitive for COVID-19 infection. Uncommon causes of acute cough should be suspected in those with HF or hay fever (allergic rhinitis) and those with occupational risk factors (such as farmworkers).

2. Persistent and chronic cough—Cough due to acute respiratory tract infection resolves within 3 weeks in more than 90% of patients. Pertussis should be considered in adolescents and adults who have persistent or severe cough lasting more than 3 weeks, who have not been adequately boosted with Tdap, and who have been exposed to a person with confirmed pertussis. It should also be considered in geographic areas where the prevalence of pertussis approaches 20% (although its exact prevalence is difficult to ascertain due to the limited sensitivity of diagnostic tests).

When ACE inhibitor use, acute respiratory tract infection, and chest radiographic abnormalities are absent, most cases of persistent and chronic cough are related to postnasal drip (upper airway cough syndrome), cough-variant asthma, or GERD, or some combination of these three entities. Approximately 10% of cases are caused by nonasthmatic eosinophilic bronchitis. A history of nasal or sinus congestion, wheezing, or heartburn should direct subsequent evaluation and treatment, though these conditions frequently cause persistent cough in the absence of typical symptoms. Dyspnea at rest or with exertion is not commonly reported among patients with persistent cough;

dyspnea requires assessment for chronic lung disease, HF, anemia, PE, or pulmonary hypertension.

Bronchogenic carcinoma is suspected when cough is accompanied by unexplained weight loss, hemoptysis, and fevers with night sweats, particularly in persons with significant tobacco or occupational exposures (asbestos, radon, diesel exhaust, and metals). Persistent and chronic cough accompanied by excessive mucus secretions increases the likelihood of COPD, particularly if there is a history of cigarette smoking, or of bronchiectasis if accompanied by a history of recurrent or complicated pneumonia; chest radiographs are helpful in diagnosis. Chronic cough with dry eyes may represent Sjögren syndrome. A chronic dry cough may be the first symptom of idiopathic pulmonary fibrosis.

B. Physical Examination

Pneumonia is suspected when acute cough is accompanied by vital sign abnormalities (tachycardia, tachypnea, fever). Findings suggestive of airspace consolidation (crackles, decreased breath sounds, fremitus, egophony) are significant predictors of community-acquired pneumonia but are present in a minority of cases. Purulent sputum is associated with bacterial infections in patients with structural lung disease (eg, COPD, cystic fibrosis), but it is a poor predictor of pneumonia in the otherwise healthy adult. Wheezing and rhonchi are frequent findings in adults with acute bronchitis and do not indicate consolidation or adult-onset asthma in most cases.

Examination of patients with persistent cough should include a search for chronic sinusitis, which may contribute to postnasal drip syndrome or to asthma. Physical examination may help distinguish COPD from HF. In patients with cough and dyspnea, a normal match test (ability to blow out a match from 25 cm away) and maximum laryngeal height greater than 4 cm (measured from the sternal notch to the cricoid cartilage at end expiration) substantially decrease the likelihood of COPD. Similarly, normal jugular venous pressure and no hepatojugular reflux decrease the likelihood of biventricular HF.

C. Diagnostic Studies

1. Acute cough—Chest radiography should be considered for any adult with acute cough whose vital signs are abnormal or whose chest examination suggests pneumonia. The relationship between specific clinical findings and the probability of pneumonia is shown in Table 2–1. A large, multicenter randomized clinical trial found that elevated serum CRP (levels greater than 30 mg/dL) improves diagnostic accuracy of clinical prediction rules for pneumonia in adults with acute cough; serum procalcitonin had only marginal utility in outpatient management (in contrast with severe pneumonia requiring hospital care). A meta-analysis found that lung ultrasonography had better accuracy than chest radiography for the diagnosis of adult community-acquired pneumonia. Lung ultrasonography had a pooled sensitivity of 0.95 and a specificity of 0.90. Chest radiography had a pooled sensitivity of 0.77 and a specificity of 0.91. In patients with dyspnea, pulse oximetry and peak flow help exclude hypoxemia or obstructive airway disease. However, a normal pulse oximetry value (eg, greater than 93%) does not rule out a significant alveolar–arterial (A–a) gradient when patients have effective respiratory compensation. During documented outbreaks, clinical diagnosis of influenza has a positive predictive value of ~70%; this usually obviates the need for rapid diagnostic tests.

Table 2–1. Positive and negative likelihood ratios of history, physical examination, and laboratory findings for the diagnosis of pneumonia.

Finding	Positive LR	Negative LR
Medical history		
Fever	1.7–2.1	0.6–0.7
Chills	1.3–1.7	0.7–0.9
Physical examination		
Tachypnea (respiratory rate > 25 breaths/min)	1.5–3.4	0.8
Tachycardia (> 100 beats/min in two studies or > 120 beats/min in one study)	1.6–2.3	0.5–0.7
Hyperthermia (> 37.8°C)	1.4–4.4	0.6–0.8
Chest examination		
Dullness to percussion	2.2–4.3	0.8–0.9
Decreased breath sounds	2.3–2.5	0.6–0.8
Crackles	1.6–2.7	0.6–0.9
Rhonchi	1.4–1.5	0.8–0.9
Egophony	2.0–8.6	0.8–1.0
Laboratory findings		
Leukocytosis (> 11,000/mcL [11 × 10^9/L] in one study or ≥ 10,400/mcL [10.4 × 10^9/L] in another study)	1.9–3.7	0.3–0.6

2. Persistent and chronic cough—Chest radiography is indicated when ACE inhibitor therapy–related and postinfectious cough are excluded. If pertussis is suspected, PCR testing should be performed on a nasopharyngeal swab or nasal wash specimen—although the ability to detect pertussis decreases as the duration of cough increases. When the chest film is normal, postnasal drip, asthma, or GERD are the most likely causes. The presence of typical symptoms of these conditions directs further evaluation or empiric therapy, though typical symptoms are often absent. Definitive tests for determining the presence of each are available (Table 2–2). However, empiric treatment with a maximum-strength regimen for postnasal drip, asthma, or GERD for 2–4 weeks is one recommended approach since documenting the presence of postnasal drip, asthma, or GERD does not mean they are the cause of the cough. Alternative approaches to identifying patients who have corticosteroid-responsive cough due to asthma include examining induced sputum for increased eosinophil counts

Table 2–2. Empiric therapy or definitive testing for persistent cough.

Suspected Condition	Step 1 (Empiric Therapy)	Step 2 (Definitive Testing)
Postnasal drip	Therapy for allergy or chronic sinusitis	Sinus CT scan; otolaryngologic referral
Asthma	Beta-2-agonist	Spirometry; consider methacholine challenge if normal
GERD	Lifestyle and diet modifications with or without PPIs	Esophageal pH monitoring

(greater than 3%) or providing an empiric trial of prednisone, 30 mg daily orally for 2 weeks.

Nonasthmatic eosinophilic bronchitis can be diagnosed by finding eosinophils with induced sputum analysis after the exclusion of other causes for chronic cough by clinical, radiologic, and lung function assessment. The cough usually responds well to inhaled corticosteroids.

Spirometry may help measure large airway obstruction (eg, foreign body or cancer) in patients who have persistent cough and wheezing and who are not responding to asthma treatment. When empiric treatment trials are not successful, additional evaluation with pH manometry, endoscopy, barium swallow, sinus CT, or high-resolution chest CT may identify the cause.

Differential Diagnosis

A. Acute Cough

Acute cough may be a symptom of acute respiratory tract infection, COVID-19, asthma, allergic rhinitis, HF, and ACE inhibitor therapy, as well as many less common causes.

B. Persistent and Chronic Cough

Causes of persistent cough include environmental exposures (cigarette smoke, air pollution), occupational exposures, pertussis, postnasal drip, asthma (including cough-variant asthma), GERD, COPD, chronic aspiration, bronchiectasis, nonasthmatic eosinophilic bronchitis, tuberculosis or other chronic infection, interstitial lung disease, and bronchogenic carcinoma. COPD is a common cause of persistent cough among patients older than 50 years who have been cigarette smokers. Persistent cough may also be due to somatic cough syndrome or tic cough, or vocal fold dysfunction.

C. Cough in the Immunocompromised Patient

The evaluation of cough in immunocompromised patients is the same as in immunocompetent patients but with an increased concern for tuberculosis (regardless of radiographic findings) as well as fungi, cytomegalovirus, varicella, herpesvirus, and *Pneumocystis jirovecii*.

Treatment

A. Acute Cough

Treatment of acute cough should target the underlying etiology of the illness, the cough reflex itself, and any additional factors that exacerbate the cough. Cough duration is typically 1–3 weeks, yet patients frequently expect cough to last fewer than 10 days. Limited studies on the use of dextromethorphan suggest a minor or modest benefit. Honey may provide symptomatic benefit.

When influenza is diagnosed (including H1N1 influenza), oral oseltamivir or zanamivir or intravenous peramivir are equally effective (1 less day of illness) when initiated within 30–48 hours of illness onset; treatment is recommended regardless of illness duration when patients have severe, complicated, or progressive influenza and in patients requiring hospitalization. In *Chlamydophila*- or *Mycoplasma*-documented infection or outbreaks, first-line antibiotics include erythromycin or doxycycline. Antibiotics do not improve cough severity or duration in patients with uncomplicated acute bronchitis. In patients with bronchitis and wheezing, inhaled beta-2-agonist therapy reduces severity and duration of cough. In patients with acute cough, treating the accompanying postnasal drip (with antihistamines, decongestants, saline nasal irrigation, or nasal corticosteroids) can be helpful. Two studies (n = 163 total patients) found codeine to be no more effective than placebo in reducing acute cough symptoms.

B. Persistent and Chronic Cough

Evaluation and management of persistent cough often require multiple visits and therapeutic trials, which frequently lead to frustration, anger, and anxiety. When pertussis infection is suspected early in its course, treatment with a macrolide antibiotic (see Chapter 33) is appropriate to reduce organism shedding and transmission. When pertussis has lasted more than 7–10 days, antibiotic treatment does not affect the duration of cough, which can last up to 6 months. Early identification, revaccination with Tdap, and treatment are encouraged for adult patients who work or live with persons at high risk for complications from pertussis (pregnant women, infants [particularly younger than 1 year], and immunosuppressed individuals).

Table 2–2 outlines empiric treatments for persistent cough. There is no evidence to guide how long to continue treatment for persistent cough due to postnasal drip, asthma, or GERD. Studies have not found a consistent benefit of inhaled corticosteroid therapy in adults with persistent cough.

There is insufficient evidence to recommend the routine use of any pharmacologic treatments (antibiotics, bronchodilators, mucolytics) as a means of relieving cough for adult patients with chronic cough due to stable chronic bronchitis.

When empiric treatment trials fail, consider other causes of chronic cough such as obstructive sleep apnea, tonsillar or uvular enlargement, and environmental fungi (see Chapter 36). The small percentage of patients with idiopathic chronic cough should be managed in

consultation with an otolaryngologist or a pulmonologist; consider a high-resolution CT scan of the lungs. Treatment options include nebulized lidocaine therapy and morphine sulfate, 5–10 mg orally twice daily. Sensory dysfunction of the laryngeal branches of the vagus nerve may contribute to persistent cough syndromes and may help explain the effectiveness of gabapentin in patients with chronic cough. Baclofen may have similar neuromodulatory action and benefit as gabapentin.

Speech pathology therapy combined with pregabalin has some benefit in chronic refractory cough. In patients with cough hypersensitivity syndrome, therapy aimed at shifting the patient's attentional focus from internal stimuli to external focal points can be helpful. PPIs are not effective when used in isolation for treating chronic cough due to gastroesophageal reflux; most benefit appears to come from lifestyle modifications and weight reduction.

When to Refer

- Failure to control persistent or chronic cough following empiric treatment trials.
- Patients with recurrent symptoms should be referred to an otolaryngologist, pulmonologist, or gastroenterologist.

When to Admit

- Patient at high risk for tuberculosis for whom compliance with respiratory precautions is uncertain.
- Need for urgent bronchoscopy, such as suspected foreign body.
- Smoke or toxic fume inhalational injury.
- Gas exchange is impaired by cough.
- Patients at high risk for barotrauma (eg, recent pneumothorax).

Kardos P et al. German Respiratory Society guidelines for diagnosis and treatment of adults suffering from acute, subacute and chronic cough. Respir Med. 2020;170:105939. [PMID: 32843157]

Malesker MA et al; CHEST Expert Cough Panel. Chronic cough due to stable chronic bronchitis: CHEST Expert Panel Report. Chest. 2020;158:705. [PMID: 32105719]

Smith MP et al; CHEST Expert Cough Panel. Acute cough due to acute bronchitis in immunocompetent adult outpatients: CHEST Expert Panel Report. Chest. 2020;157:1256. [PMID: 32092323]

DYSPNEA

ESSENTIAL INQUIRIES

- Fever, cough, risk of COVID-19, and chest pain.
- Vital sign measurements; pulse oximetry.
- Cardiac and chest examination.
- Chest radiography and arterial blood gas measurement in selected patients.

General Considerations

Dyspnea is a subjective experience or perception of uncomfortable breathing. The relationship between level of dyspnea and the severity of underlying disease varies widely among individuals. Dyspnea can result from conditions that increase the mechanical effort of breathing (eg, asthma, COPD, restrictive lung disease, respiratory muscle weakness), alveolar lung disease (pulmonary edema, pneumonia, alveolar proteinosis), conditions that produce compensatory tachypnea (eg, hypoxemia, acidosis), primary pulmonary vasculopathy (pulmonary hypertension), or psychogenic conditions.

Clinical Findings

A. Symptoms

The duration, severity, and periodicity of dyspnea influence the tempo of the clinical evaluation. Rapid onset or severe dyspnea in the absence of other clinical features should raise concern for pneumothorax, PE, or increased left ventricular end-diastolic pressure (LVEDP).

Spontaneous pneumothorax is usually accompanied by chest pain and occurs most often in thin, young males and in those with underlying lung disease. PE should always be suspected when a patient with new dyspnea reports a recent history (previous 4 weeks) of prolonged immobilization or surgery, estrogen therapy, or other risk factors for DVT (eg, previous history of thromboembolism, cancer, obesity, lower extremity trauma) and when the cause of dyspnea is not apparent. Silent MI, which occurs more frequently in persons with diabetes and women, can result in increased LVEDP, acute HF, and dyspnea.

Accompanying symptoms provide important clues to causes of dyspnea. When cough and fever are present, pulmonary disease (particularly infection) is the primary concern; myocarditis, pericarditis, and septic emboli can also present in this manner. Chest pain should be further characterized as acute or chronic, pleuritic or exertional. Although acute pleuritic chest pain is the rule in acute pericarditis and pneumothorax, most patients with pleuritic chest pain in the outpatient clinic have pleurisy due to acute viral respiratory tract infection. Periodic chest pain that precedes the onset of dyspnea suggests myocardial ischemia or PE. Most cases of dyspnea associated with wheezing are due to acute bronchitis; however, other causes include new-onset asthma, foreign body, and vocal fold dysfunction. Interstitial lung disease and pulmonary hypertension should be considered in patients with symptoms (or history) of connective tissue disease. Pulmonary lymphangitic carcinomatosis should be considered if a patient has a malignancy, especially breast, lung, or gastric cancer.

When a patient reports prominent dyspnea with mild or no accompanying features, consider noncardiopulmonary causes of impaired oxygen delivery (anemia, methemoglobinemia, cyanide ingestion, carbon monoxide poisoning), metabolic acidosis, panic disorder, neuromuscular disorders, and chronic PE.

Platypnea-orthodeoxia syndrome is characterized by dyspnea and hypoxemia on sitting or standing that

improves in the recumbent position. Hyperthyroidism can cause dyspnea from increased ventilatory drive, respiratory muscle weakness, or pulmonary hypertension. Patients in whom moderate to severe SARS-CoV-2 disease develops typically have 4–10 days of upper respiratory infection symptoms followed by a precipitous increase in dyspnea. Patients who recover from their initial COVID-19 infection may have persistent dyspnea as part of the "long COVID" syndrome.

B. Physical Examination

A focused physical examination should include evaluation of the head and neck, chest, heart, and lower extremities. Visual inspection of the patient can suggest obstructive airway disease (pursed-lip breathing, use of accessory respiratory muscles, barrel-shaped chest), pneumothorax (asymmetric excursion), or metabolic acidosis (Kussmaul respirations). Patients with impending upper airway obstruction (eg, epiglottitis, foreign body) or severe asthma exacerbation sometimes assume a tripod position. Focal wheezing raises the suspicion for a foreign body or other bronchial obstruction. Maximum laryngeal height (the distance between the top of the thyroid cartilage and the suprasternal notch at end expiration) is a measure of hyperinflation. Obstructive airway disease is virtually nonexistent when a nonsmoking patient younger than age 45 years has a maximum laryngeal height greater than 4 cm.

Factors increasing the likelihood of obstructive airway disease (in patients without known obstructive airway disease) include patient history of more than 40 pack-years smoking (adjusted LR+ 11.6; LR– 0.9), patient age 45 years or older (LR+ 1.4; LR– 0.5), and maximum laryngeal height greater than or equal to 4 cm (LR+ 3.6; LR– 0.7). With all three of these factors present, the LR+ rises to 58.5 and the LR– falls to 0.3.

Absent breath sounds suggest a pneumothorax. An accentuated pulmonic component of the second heart sound (loud P_2) is a sign of pulmonary hypertension and PE.

Clinical predictors of increased LVEDP in dyspneic patients with no prior history of HF include tachycardia, systolic hypotension, jugular venous distention, hepatojugular reflux, bibasilar crackles, third heart sound, lower extremity edema, and chest film findings of pulmonary vascular redistribution or cardiomegaly. When none is present, there is a very low probability (less than 10%) of increased LVEDP, but when two or more are present, there is a very high probability (greater than 90%) of increased LVEDP.

C. Diagnostic Studies

Causes of dyspnea that can be managed without chest radiography are few: anemia, carbon monoxide poisoning, and ingestions causing lactic acidosis and methemoglobinemia. The diagnosis of pneumonia should be confirmed by chest radiography in most patients, and elevated blood levels of procalcitonin or CRP can support the diagnosis of pneumonia in equivocal cases or in the presence of interstitial lung disease. Conversely, a low procalcitonin can help exclude pneumonia in dyspneic patients presenting with HF.

Chest radiography is fairly sensitive and specific for new-onset HF (represented by redistribution of pulmonary venous circulation) and can help guide treatment of patients with other cardiac diseases. NT-proBNP can assist in the diagnosis of HF (see below). End-expiratory chest radiography enhances detection of small pneumothoraces. A systematic review of five randomized controlled trials and 44 prospective cohort-type studies in patients with acute dyspnea assessed point-of-care ultrasonography (POCUS) as a diagnostic tool to determine the underlying cause of dyspnea. When added to a standard diagnostic pathway, POCUS led to statistically significantly more correct diagnoses in patients with dyspnea than the standard diagnostic pathway. POCUS consistently improved the sensitivities of standard diagnostic pathways to detect HF, pneumonia, PE, pleural effusion, or pneumothorax. Specificities increased in most studies; in-hospital mortality and length of hospital stay, however, did not differ significantly between patients who did or did not receive POCUS in addition to standard diagnostic tests.

A normal chest radiograph has substantial diagnostic value. When there is no physical examination evidence of COPD or HF and the chest radiograph is normal, the major remaining causes of dyspnea include PE, *P jirovecii* infection (the initial radiograph may be normal in up to 25%), upper airway obstruction, foreign body, anemia, and metabolic acidosis. If a patient has tachycardia or hypoxemia but a normal chest radiograph and ECG, then tests to exclude pulmonary emboli, anemia, or metabolic acidosis are warranted. High-resolution chest CT is particularly useful in the evaluation of interstitial and alveolar lung disease. Helical ("spiral") CT is useful to diagnose PE since the images are high resolution and require only one breath-hold by the patient, but to minimize unnecessary testing and radiation exposure, the clinician should first consider a clinical decision rule (with or without D-dimer testing) to estimate the pretest probability of a PE. It is appropriate to forego CT scanning in patients with very low probability of pulmonary embolus when other causes of dyspnea are more likely (see Chapter 9).

Laboratory findings suggesting increased LVEDP include elevated serum BNP or NT-proBNP levels. BNP has been shown to reliably diagnose severe dyspnea caused by HF and to differentiate it from dyspnea due to other conditions.

Arterial blood gas measurement may be considered if clinical examination and routine diagnostic testing are equivocal. With two notable exceptions (carbon monoxide poisoning and cyanide toxicity), arterial blood gas measurement distinguishes increased mechanical effort causes of dyspnea (respiratory acidosis with or without hypoxemia) from compensatory tachypnea (respiratory alkalosis with or without hypoxemia or metabolic acidosis) and from psychogenic dyspnea (respiratory alkalosis). Carbon monoxide and cyanide impair oxygen delivery with minimal alterations in Po_2; percent carboxyhemoglobin identifies carbon monoxide toxicity. Cyanide poisoning should be considered in a patient with profound lactic acidosis following exposure to burning vinyl (such as a theater fire or industrial accident). Suspected carbon monoxide

poisoning or methemoglobinemia can also be confirmed with venous carboxyhemoglobin or methemoglobin levels. Venous blood gas testing is also an option for assessing acid-base and respiratory status by measuring venous pH and Pco_2 but is unable to provide information on oxygenation status. To correlate with arterial blood gas values, venous pH is typically 0.03–0.05 units lower, and venous Pco_2 is typically 4–5 mm Hg higher than arterial samples.

Because arterial blood gas testing is impractical in most outpatient settings, pulse oximetry has a central role in the office evaluation of dyspnea. Oxygen saturation values above 96% almost always correspond with a Po_2 greater than 70 mm Hg, whereas values less than 94% may represent clinically significant hypoxemia. Important exceptions to this rule include carbon monoxide toxicity, which leads to a normal oxygen saturation (due to the similar wavelengths of oxyhemoglobin and carboxyhemoglobin), and methemoglobinemia, which results in an oxygen saturation of about 85% that fails to increase with supplemental oxygen. Pulse oximetry to detect occult hypoxia is less accurate in Black patients (OR, 2.57) compared to White patients. A delirious or obtunded patient with obstructive lung disease warrants immediate measurement of arterial blood gases to exclude hypercapnia and the need for intubation, regardless of the oxygen saturation. If a patient reports dyspnea with exertion, but resting oximetry is normal, assessment of desaturation with ambulation (eg, a brisk walk around the clinic) can be useful for confirming impaired gas exchange. Persons with COVID-19 may have low oxygen saturation with minimal dyspnea and profound desaturation with minimal exertion.

A study found that for adults without known cardiac or pulmonary disease reporting dyspnea on exertion, spirometry, NT-proBNP, and CT imaging were the most informative tests.

Episodic dyspnea can be challenging if an evaluation cannot be performed during symptoms. Life-threatening causes include recurrent PE, myocardial ischemia, and reactive airway disease. When associated with audible wheezing, vocal fold dysfunction should be considered, particularly in a young woman who does not respond to asthma therapy. Spirometry is very helpful in further classifying patients with obstructive airway disease but is rarely needed in the initial or emergent evaluation of patients with acute dyspnea.

Differential Diagnosis

Urgent and emergent conditions causing acute dyspnea include pneumonia, COPD, asthma, pneumothorax, PE, cardiac disease (eg, HF, acute MI, valvular dysfunction, arrhythmia, intracardiac shunt), pleural effusion, COVID-19, diffuse alveolar hemorrhage, metabolic acidosis, cyanide toxicity, methemoglobinemia, and carbon monoxide poisoning. Chronic dyspnea may be caused by interstitial lung disease, pulmonary hypertension, or pulmonary alveolar proteinosis.

Treatment

The treatment of urgent or emergent causes of dyspnea should aim to relieve the underlying cause. Pending diagnosis, patients with hypoxemia should be immediately provided supplemental oxygen unless significant hypercapnia is present or strongly suspected pending arterial blood gas measurement. Dyspnea frequently occurs in patients nearing the end of life. Opioid therapy, anxiolytics, and corticosteroids can provide substantial relief independent of the severity of hypoxemia. However, inhaled opioids are not effective.

Oxygen therapy is most beneficial to patients with significant hypoxemia (Pao_2 less than 55 mm Hg) (see Chapter 5). In patients with severe COPD and hypoxemia, oxygen therapy improves exercise performance and mortality. Pulmonary rehabilitation programs are another therapeutic option for patients with moderate to severe COPD or interstitial pulmonary fibrosis. Noninvasive ventilation may be considered for patients with dyspnea caused by an acute COPD exacerbation.

When to Refer

- Following acute stabilization, patients with advanced COPD should be referred to a pulmonologist, and patients with HF or valvular heart disease should be referred to a cardiologist.
- Cyanide toxicity or carbon monoxide poisoning should be managed in conjunction with a toxicologist.
- Lung transplantation can be considered for patients with advanced interstitial lung disease.

When to Admit

- Impaired gas exchange from any cause or high risk of PE pending definitive diagnosis.
- Suspected cyanide toxicity or carbon monoxide poisoning.

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Valbuena VSM et al. Racial bias in pulse oximetry measurement among patients about to undergo ECMO in 2019–2020, a retrospective cohort study. Chest. 2021 Sep 27. [Epub ahead of print] [PMID: 34592317]

HEMOPTYSIS

ESSENTIAL INQUIRIES

- Fever, cough, and other symptoms of lower respiratory tract infection.
- Smoking history.
- Nasopharyngeal or GI bleeding.
- Chest radiography and CBC (and, in some cases, INR).

General Considerations

Hemoptysis is the expectoration of blood that originates below the vocal folds. It is commonly classified as trivial, mild, or massive—the latter defined as more than 200–600 mL (about 1–2 cups) in 24 hours. Massive hemoptysis can be usefully defined as any amount that is hemodynamically significant or threatens ventilation. Its in-hospital mortality was 6.5% in one study. The initial goal of management of massive hemoptysis is therapeutic, not diagnostic.

The causes of hemoptysis can be classified anatomically. Blood may arise from the upper airway due to malignant invasion or foreign body; from the airways in COPD, bronchiectasis, bronchial Dieulafoy disease, and bronchogenic carcinoma; from the pulmonary vasculature in LV failure, mitral stenosis, PE, pulmonary arterial hypertension, telangiectasias, arteriovenous malformations, and multiple pulmonary artery aneurysms; from the systemic circulation in intralobar pulmonary sequestration, aortobronchial fistula; or from the pulmonary parenchyma in pneumonia, fungal infections, inhalation of crack cocaine, granulomatosis with polyangiitis, or Takayasu arteritis with pulmonary arteritis. Hemoptysis can be caused by the parasitic diseases paragonimiasis (most common cause worldwide) and human echinococcosis (also called hydatid disease). Diffuse alveolar hemorrhage—manifested by alveolar infiltrates on chest radiography—is due to small vessel bleeding usually caused by autoimmune or hemostatic disorders, or rarely precipitated by hypertensive emergency or anticoagulant therapy. Most cases of hemoptysis presenting in the outpatient setting are due to infection (eg, acute or chronic bronchitis, pneumonia, tuberculosis, infection with *Mycobacterium avium* complex, aspergillosis). Hemoptysis due to lung cancer increases with age, causing up to 20% of cases among older adults. Pulmonary venous hypertension (eg, mitral stenosis, PE) causes hemoptysis in less than 10% of cases. Most cases of hemoptysis that have no visible cause on CT scan or bronchoscopy will resolve within 6 months without treatment, with the notable exception of patients at high risk for lung cancer (patients who smoke cigarettes and are older than 40 years). Iatrogenic hemorrhage may follow transbronchial lung biopsies, anticoagulation, or pulmonary artery rupture due to distal placement of a balloon-tipped catheter. Obstructive sleep apnea with elevated pulmonary arterial pressure may be a risk factor for hemoptysis. Amyloidosis of the lung can cause hemoptysis, as can endometriosis. No cause is identified in up to 15–30% of cases.

Clinical Findings

A. Symptoms

Blood-tinged sputum in the setting of an upper respiratory tract infection in an otherwise healthy, young (age under 40 years) nonsmoker does not warrant an extensive diagnostic evaluation if the hemoptysis subsides with resolution of the infection. However, hemoptysis is frequently a sign of serious disease, especially in patients with a high prior probability of underlying pulmonary pathology. Hemoptysis is the only symptom found to be a specific predictor of lung cancer. It portends a high risk of mortality in COVID-19 infection. There is no value in distinguishing blood-streaked sputum and cough productive of blood during evaluation; the goal of the history is to identify patients at risk for one of the disorders listed earlier. Pertinent features include duration of symptoms, presence of respiratory infection, and past or current tobacco use. Nonpulmonary sources of hemorrhage—from the sinuses or the GI tract—must be excluded.

B. Physical Examination

Elevated pulse, hypotension, and decreased oxygen saturation suggest large-volume hemorrhage that warrants emergent evaluation and stabilization. The nares and oropharynx should be carefully inspected to identify a potential upper airway source of bleeding. Chest and cardiac examination may reveal evidence of HF or mitral stenosis.

C. Diagnostic Studies

Diagnostic evaluation should include a chest radiograph and CBC. Kidney function tests, UA, and coagulation studies are appropriate in specific circumstances. Hematuria that accompanies hemoptysis may be a clue to antibasement membrane antibody disease or vasculitis. Flexible bronchoscopy reveals endobronchial cancer in 3–6% of patients with hemoptysis who have a normal (non-lateralizing) chest radiograph. Nearly all these patients are cigarette smokers over the age of 40, and most will have had symptoms for more than 1 week. High-resolution chest CT scan complements bronchoscopy; it can visualize unsuspected bronchiectasis and arteriovenous malformations and will show central endobronchial cancers in many cases. It is the test of choice for suspected small peripheral malignancies. Helical pulmonary CT angiography is the initial test of choice for evaluating patients with suspected PE, although caution should be taken to avoid large contrast loads in patients with even mild CKD (serum creatinine greater than 2.0 g/dL or rapidly rising creatinine in normal range). Helical CT scanning can be avoided in patients who are at "unlikely" risk for PE using the Wells score or PERC (Pulmonary Embolism Rule-Out Criteria) rule for PE and the sensitive D-dimer test (see Chapter 9). Echocardiography may reveal evidence of HF or mitral stenosis. Multidetector CT angiography is the study of choice to determine the location, etiology, and mechanism of the bleeding.

Treatment

Management of mild hemoptysis consists of identifying and treating the specific cause. Massive hemoptysis is life-threatening. The airway should be protected with endotracheal intubation, ventilation ensured, and effective circulation maintained. If the location of the bleeding site is known, the patient should be placed in the decubitus position with the involved lung dependent. Uncontrollable hemorrhage warrants rigid bronchoscopy and surgical consultation. In stable patients, flexible bronchoscopy may localize the site of bleeding, and angiography can embolize the involved bronchial arteries. Embolization is effective initially in 85% of cases, although rebleeding may occur in

up to 20% of patients during the following year. The anterior spinal artery arises from the bronchial artery in up to 5% of people, and paraplegia may result if it is inadvertently cannulated and embolized.

One double-blind, randomized controlled trial compared treatment with inhalations of tranexamic acid (an antifibrinolytic drug) versus placebo (normal saline) in patients hospitalized with mild hemoptysis (less than 200 mL of expectorated blood per 24 hours). Compared to patients receiving placebo (normal saline), more patients treated with tranexamic acid experienced resolution of hemoptysis within 5 days of admission (96% versus 50%). In addition, mean hospital length of stay was shorter for the tranexamic acid group, and fewer patients required invasive procedures (interventional bronchoscopy, angiographic embolization) to control the hemorrhage. Another randomized study found that compared to the control group, patients given tranexamic acid on admission had significantly lower in-hospital mortality (11.5% versus 9.0%).

When to Refer

- Refer to a pulmonologist when bronchoscopy of the lower respiratory tract is needed.
- Refer to an otolaryngologist when an upper respiratory tract bleeding source is identified.
- Refer to a hematologist when severe coagulopathy complicates management.

When to Admit

- To stabilize bleeding process in patients at risk for or experiencing massive hemoptysis.
- To correct disordered coagulation (using clotting factors or platelets, or both) or to reverse anticoagulation.
- To stabilize gas exchange.

Davidson K et al. Managing massive hemoptysis. Chest. 2020;157:77. [PMID: 31374211]
Kinoshita T et al. Effect of tranexamic acid on mortality in patients with haemoptysis: a nationwide study. Crit Care. 2019;23:347. [PMID: 31694697]

CHEST PAIN

ESSENTIAL INQUIRIES

- Pain onset, character, location/size, duration, periodicity, and exacerbators; shortness of breath.
- Vital signs; chest and cardiac examinations.
- ECG and biomarkers of myocardial necrosis in selected patients.

General Considerations

Chest pain (or chest discomfort) can occur as a result of cardiovascular, pulmonary, pleural, or musculoskeletal disease; esophageal or other GI disorders; herpes zoster; cocaine use; or anxiety states. The frequency and distribution of life-threatening causes of chest pain, such as acute coronary syndrome (ACS), pericarditis, aortic dissection, vasospastic angina, PE, pneumonia, and esophageal perforation, vary substantially between clinical settings.

SLE, rheumatoid arthritis, reduced eGFR, and HIV infection are conditions that confer a strong risk of CAD. Precocious ACS (occurring in patients aged 35 years or younger) may represent acute thrombosis independent of underlying atherosclerotic disease. Risk factors for precocious ACS are obesity, hyperlipidemia, and smoking.

Although ACS presents with a broader range of symptoms in women than men, specific chest pain characteristics of acute MI do not differ in frequency or strength between men and women.

Because PE can present with a wide variety of symptoms, consideration of the diagnosis and rigorous risk factor assessment for venous thromboembolism (VTE) is critical. Classic VTE risk factors include cancer, trauma, recent surgery, prolonged immobilization, pregnancy, oral contraceptives, and family history and prior history of VTE. Other conditions associated with increased risk of PE include HF and COPD. Sickle cell anemia can cause acute chest syndrome. Patients with this syndrome often have chest pain, fever, and cough.

Clinical Findings

A. Symptoms

Myocardial ischemia is usually described as a dull, aching sensation of "pressure," "tightness," "squeezing," or "gas," rather than as sharp or spasmodic. Pain reaching maximum intensity in seconds is uncommon. Ischemic symptoms usually subside within 5–20 minutes but may last longer. Progressive symptoms or symptoms at rest may represent unstable angina. Up to one-third of patients with acute MI do not report chest pain. Chest pain is present in more than 90% of patients having a STEMI who are under age 65 but in only 57% of patients having a STEMI who are over age 85.

Continuous chest pain lasting 24 hours or longer is unlikely due to an acute MI (LR, 0.15). However, chest pain lasting 1 minute or less does not exclude MI (LR, 0.95). When present, pain due to myocardial ischemia is commonly accompanied by a sense of anxiety or uneasiness. The location is usually retrosternal or left precordial. Because the heart lacks somatic innervation, precise localization of pain due to cardiac ischemia is difficult; the pain is commonly referred to the throat, lower jaw, shoulders, inner arms, upper abdomen, or back. Ischemic pain may be precipitated or exacerbated by exertion, cold temperature, meals, stress, or combinations of these factors and is usually relieved by rest. However, many episodes do not conform to these patterns, and a broader range of symptoms of ACS are more common in older adults, women, and persons with diabetes mellitus. Other symptoms that are associated with ACS include shortness of breath; dizziness; a feeling of impending doom; and vagal symptoms, such as nausea and diaphoresis. In older persons, fatigue is a common presenting complaint of ACS.