Handbook of Outpatient Medicine

Elana Sydney ·
Eleanor Weinstein ·
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Second Edition

Springer

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We dedicate this book to our patients who have taught us so much over the years.

Preface

The practice of medicine in the outpatient setting has become increasingly complex and challenging in recent years. Pressures of time and of decision-making regarding patients with multiple comorbidities may test even the most-seasoned clinicians. The busy clinician needs an easy-to-use, quick reference that can help guide assessments and therapeutic plans on the spot. As practicing general internists and teachers for decades, we know very well how critical it is to have a clear idea quickly about how to approach the patient sitting across from you in the exam room. Our goal of revising the first edition of *Handbook of Outpatient Medicine*, originally published in 2018, was to provide an updated roadmap for the common problems that present themselves to the outpatient adult provider.

This book is organized into several sections. The first section deals with the approach to special populations, such as the older adult and the teen with chronic medical problems transitioning to adult care. The remaining sections focuse on specific symptoms, diagnoses, and organ systems. Each chapter includes an algorithm to efficiently guide the user along the decision points of making the diagnosis and/ or determining the best treatment. The sections are written by experienced outpatient clinicians and based on current evidence and up-to-date recommendations by respected organizations such as the US Preventive Services Task Force.

Quotidian topics like diabetes and hypertension are presented in more detail. Other common issues less reliably included in textbooks are covered here as well. These topics include obesity, sleep apnea, hair loss, and new to this second

edition, post-covid care, and addiction medicine. Although this book is certainly not intended to be an exhaustive compendium of medicine, it does address most of the diagnoses and chief complaints presented to an outpatient internal medicine practitioner. Additionally, the approach to diagnosis and treatment represents a variety of medical centers across the country as well as internationally.

Written and organized in an easy-to-follow style, this book can aid physicians, medical students, nurse practitioners, and physician assistants. We hope you find this reference to be useful.

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Joseph Conigliaro and Sandeep Kapoor

Introduction

Traditional medical pedagogy stresses the importance of a complete patient history and physical exam. Though this is extremely relevant for the purposes of learning and perfecting skills, the reality of clinical practice does not allow the clinician to complete a full examination at each patient visit. Therefore, clinicians need to decide how to narrow the focus. When is it appropriate to perform focused history taking and examinations? What can the clinician use to guide these decisions? Evidence-based recommendations for screening can support the decision process and help guide the content of the encounter with the patient and the care provided. This chapter will highlight the importance of **prevention**, **harm reduction**, and thoughtful **screening** to better inform the physical examination and health maintenance planning.

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Intersection of Public Health and Primary Care

Public health and epidemiology provide insights into the prevalence of diseases and conditions in different populations. Public health focuses on prevention of disease and health promotion rather than the diagnosis and treatment of diseases. The equation of one's overall well-being is now understood to be influenced by many factors, including but not limited to the social, environmental and economic, as well as one's education, employment, healthcare access, genetics, and health behaviors. The intersection of public health and primary care is one that requires exploration, reflection, strategy, and action.

Social Determinants of Health (SDOH) [1]

The World Health Organization (WHO) defines social determinants of health as "The conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies and political systems" [2]. Addressing social determinants is an important and ever-developing area of practice that entails starting earlier and broadening the scope of interventions, thus making entire families and communities healthier [3].

Evidence and personal experiences have validated that quality of life, physical and mental health, and overall well-being are impacted by SDOH and that healthcare teams have the power to manifest equity of care. To do so demands understanding, compassion, and skill. The following domains can be explored in a timely fashion to better understand a patient's circumstances: housing, transportation, and neighborhoods; racism, discrimination, and violence; education, job opportunities, and income; access to nutritious foods and physical activity opportunities; purity of air and water; and language and literacy skills [1]. Acknowledgment of individuals, in a holistic manner, is key to partnership and co-navigation toward better health outcomes.

Prevention

Prevention activities are crucial in defining policies, guidelines, and clinical approaches. The Centers for Disease Control and Prevention (CDC) deconstructs the landscape of prevention into three categories [4]:

- *Primary prevention*: intervening *before* health effects occur, through measures such as vaccinations, altering risky behaviors (poor eating habits, tobacco use), and banning substances known to be associated with a disease or health condition [4].
- *Secondary prevention*: screening to *identify* diseases in the earliest stages, before the onset of signs and symptoms,

through measures such as mammography and regular blood pressure measurement [4].
- *Tertiary prevention*: managing disease post-diagnosis to *slow or stop* disease progression through measures such as chemotherapy, rehabilitation, and continued screening for complications [4].

Harm Reduction

Harm reduction refers to interventions aimed at reducing the negative effects of health behaviors without necessarily extinguishing the problematic health behaviors completely or permanently. The term "harm reduction" is tightly and traditionally associated with substance and tobacco use [5, 6]; however the philosophy of harm reduction can be applied to all health behaviors where reduction of harm can be sought via mitigated and measured behavioral change.

The principles of harm reduction in healthcare settings [7] can serve to orient one's personal mindset on how to approach this perspective (Table 1.1) and how to apply to a prevalent health disorder such as obesity (Table 1.2).

Table 1.1 Harm reduction principles, definitions, and approaches for healthcare settings [7]

Principle	Definition	Approaches
1. Humanism	• Providers value, care for, respect, and dignify patients as individuals • It is important to recognize that people do things for a reason; harmful health behaviors provide some benefit to the individual, and those benefits must be assessed and acknowledged to understand the balance between harms and benefits • Understanding why patients make decisions is empowering for providers	• Moral judgments made against patients do not produce positive health outcomes • Grudges are not held against patients • Services are user-friendly and responsive to patients' needs • Providers accept patients' choices
2. Pragmatism	• None of us will ever achieve perfect health behaviors • Health behaviors and the ability to change them are influenced by social and community norms; behaviors do not occur within a vacuum	• Abstinence is neither prioritized nor assumed to be the goal of the patient • A range of supportive approaches is provided • Care messages should be about actual harms to patients as opposed to moral or societal standards • It is valuable for providers to understand that harm reduction can present experiences of moral ambiguity, since they are essentially supporting individuals in health behaviors that are likely to result in negative health outcomes

(continued)

TABLE 1.1 (continued)

Principle	Definition	Approaches
3. Individualism	• Every person presents with his/her own needs and strengths • People present with spectrums of harm and receptivity and therefore require a spectrum of intervention options	• Strengths and needs are assessed for each patient, and no assumptions are made based on harmful health behaviors • There is not a universal application of protocol or messaging for patients Instead, providers tailor messages and interventions for each patient and maximize treatment options for each patient served
4. Autonomy	• Though providers offer suggestions and education regarding patients' medications and treatment options, individuals ultimately make their own choices about medications, treatment, and health behaviors to the best of their abilities, beliefs, and priorities	• Provider-patient partnerships are important, and these are exemplified by patient-driven care, shared decision-making, and reciprocal learning • Care negotiations are based on the current state of the patient

5. Incrementalism	• Any positive change is a step toward improved health, and positive change can take years • It is important to understand and plan for backward movements	• Providers can help patients celebrate any positive movement • It is important to recognize that at times, all people experience plateaus or negative trajectories • Providing positive reinforcement is valuable
6. Accountability without termination	• Patients are responsible for their choices and health behaviors • Patients are not "fired" for not achieving goals • Individuals have the right to make harmful health decisions, and providers can still help them to understand that the consequences are their own	• While helping patients to understand the impact of their choices and behaviors is valuable, backward movement is not penalized

Table 1.2 Examples of application of harm reduction principles for patients who are obese [7]

Principle	Example
1. Humanism	• Providers do not shame or think less of patients with obesity • Providers strive to understand underlying factors contributing to patients' obesity, which may include lack of access to healthy food or unhealthy eating habits that are rooted in family traditions or local culture • Clinicians do not impose their personal beliefs about diet upon patients who are overweight or assume that weight loss is the patients' prioritized goal
2. Pragmatism	• Providers do not expect that the obese patient will never eat processed or sugary foods again • Behavioral interventionists encourage patients to reduce their consumption of processed or high-fat, low-nutrition foods • Rather than mandating that patients must lose a specific amount of weight, providers work with patients to establish realistic eating goals, which may or may not include weight goals
3. Individualism	• In working with patients who are obese, providers might strive to understand the patient's experience and how it contributes to suboptimal health and then offer appropriate interventions. For example, food vouchers or referrals to food pantries with fresh produce might be a useful support for patients without access to healthy food

4. Autonomy	• In working with overweight patients, providers might assess readiness to lose weight and provide patients with health improvement education and options • Providers support their patients in developing plans to implement health-promoting strategies that are acceptable to the patient, such as adding exercise intervals or incorporating fresh produce into their diets
5. Incrementalism	• For the obese patient, any weight loss, increase in physical activity, or improvement in other clinical markers is seen as success • For patients who overeat, healthy eating is viewed as an ongoing, gradual process • For patients who are interested in losing weight, weight gain is not seen as failure but as part of the process
6. Accountability without termination	• Patients who are overweight and have diabetes continue to receive insulin even though they regularly eat foods with high-sugar content • Patients who are obese are not terminated from care if they continue to gain weight

Decision-Making/Differential Diagnosis

Screening

The utilization of sensitive and specific screening tools can serve to guide the decision-making process and the formulation of differential diagnoses. Screenings are utilized to help identify early-stage disease processes where early identification and treatment have been demonstrated to improve outcomes. Safety, risk, cost-effectiveness, and predictive value need to be considered when deciding which screenings are to be conducted in which populations.

Screening is constant throughout the care of the patient. The action of screening exists while co-constructing a history, while conducting a physical exam and beyond a visit when reviewing laboratory results. Clinicians are charged with investigating relevant nuggets of information that may align with an illness profile, and to satisfy this expectation, they need to arm themselves with screening tools that can facilitate the process.

The US Preventive Services Task Force (USPSTF) is an independent panel of experts in primary care and prevention [8]. This panel systematically reviews the literature for evidence of effectiveness and develops recommendations for clinical preventive services. The USPSTF highlights over 45 "A-" and "B-" rated recommendations based on a patient's gender, age, and certain risk factors (Table 1.3) [9]. The task force assigns one of five letter grades (A, B, C, D, or I) to each recommendation based on the evidence of effectiveness (Table 1.4) [10]. These recommendations are updated periodically.

Clinicians are accustomed to a multitude of evidence-based screenings that are already part of the usual clinical care (e.g., blood pressure, weight, HbA1c, hepatitis, HIV testing, etc.). In addition, the USPSTF and other similar panels make recommendations for screening for behavioral conditions and risky behaviors such as depression [11], sedentary lifestyle, and alcohol use [12]. These recommendations

Table 1.3 USPSTF "A-" and "B-" rated recommendations [9]

Topic	Description	Grade	Release date of current recommendation
Abdominal aortic aneurysm: screening: men aged 65–75 years who have ever smoked	The USPSTF recommends one-time screening for abdominal aortic aneurysm (AAA) with ultrasonography in men aged 65–75 years who have ever smoked	B	December 2019[a]
Aspirin use to prevent cardiovascular disease and colorectal cancer: preventive medication: adults aged 50–59 years with a 10% or greater 10-year CVD risk	The USPSTF 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	April 2016[a]
Aspirin use to prevent preeclampsia and related morbidity and mortality: preventive medication: pregnant persons at high risk for preeclampsia	The USPSTF recommends the use of low-dose aspirin (81 mg/day) as preventive medication after 12 weeks of gestation in persons who are at high risk for preeclampsia. See the Practice Considerations section for information on high risk and aspirin dose	B	September 2021[a]

(continued)

Table 1.3 (continued)

Topic	Description	Grade	Release date of current recommendation
Asymptomatic bacteriuria in adults: screening: pregnant persons	The USPSTF recommends screening for asymptomatic bacteriuria using urine culture in pregnant persons	B	September 2019[a]
BRCA-related cancer: risk assessment, genetic counseling, and genetic testing: women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with brca1/2 gene mutation	The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (BRCA1/2) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing	B	August 2019[a]
Breast cancer: medication use to reduce risk: women at increased risk for breast cancer aged 35 years or older	The USPSTF recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects	B	September 2019[a]

Breast cancer: Sscreening: women aged 50–74 years	The USPSTF recommends biennial screening mammography for women aged 50–74 years	B	January 2016[a]
Breastfeeding: primary care interventions: pregnant women, new mothers, and their children	The USPSTF recommends providing interventions during pregnancy and after birth to support breastfeeding	B	October 2016[a]
Cervical Cancer: Screening: women aged 21–65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women aged 21–29 years. For women aged 30–65 years, the USPSTF recommends screening every 3 years with cervical cytology alone, every 5 years with high-risk human papillomavirus (hrHPV) testing alone, or every 5 years with hrHPV testing in combination with cytology (cotesting). See the Clinical Considerations section for the relative benefits and harms of alternative screening strategies for women 21 years or older	A	August 2018[a]
Chlamydia and gonorrhea: Sscreening: sexually active women, including pregnant persons	The USPSTF recommends screening for gonorrhea in all sexually active women 24 years or younger and in women 25 years or older who are at increased risk for infection	B	September 2021[a]

(continued)

Table 1.3 (continued)

Topic	Description	Grade	Release date of current recommendation
Chlamydia and gonorrhea: screening: sexually active women, including pregnant persons	The USPSTF recommends screening for chlamydia in all sexually active women 24 years or younger and in women 25 years or older who are at increased risk for infection	B	September 2021[a]
Colorectal cancer: screening: adults aged 45–49 years	The USPSTF recommends screening for colorectal cancer in adults aged 45–49 years. See the “"Practice Considerations” section and Table 1.1 for details about screening strategies	B	May 2021[a]
Colorectal cancer: Sscreening: adults aged 50–75 years	The USPSTF recommends screening for colorectal cancer in all adults aged 50–75 years. See the “"Practice Considerations” section and Table 1.1 for details about screening strategies	A	May 2021[a]
Depression in adults: screening: general adult population, including pregnant and postpartum women	The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up	B	January 2016[a]

Depression in children and adolescents: screening: adolescents aged 12–18 years	The USPSTF recommends screening for major depressive disorder (MDD) in adolescents aged 12–18 years. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up	B	February 2016[a]
Falls prevention in community-dwelling older adults: interventions: adults 65 years or older	The USPSTF recommends exercise interventions to prevent falls in community-dwelling adults 65 years or older who are at increased risk for falls	B	April 2018[a]
Folic acid for the prevention of neural tube defects: preventive medication: women who are planning or capable of pregnancy	The USPSTF recommends that all women who are planning or capable of pregnancy take a daily supplement containing 0.4–0.8 mg (400–800 μg) of folic acid	A	January 2017[a]
Gestational diabetes: screening: asymptomatic pregnant persons at 24 weeks of gestation or after	The USPSTF recommends screening for gestational diabetes in asymptomatic pregnant persons at 24 weeks of gestation or after	B	August 2021[a]

(continued)

Table 1.3 (continued)

Topic	Description	Grade	Release date of current recommendation
Healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: behavioral counseling interventions: adults with cardiovascular disease risk factors	The USPSTF recommends offering or referring adults with cardiovascular disease risk factors to behavioral counseling interventions to promote a healthy diet and physical activity	B	November 2020[a]
Healthy weight and weight gain in pregnancy: behavioral counseling interventions: pregnant persons	The USPSTF recommends that clinicians offer pregnant persons effective behavioral counseling interventions aimed at promoting healthy weight gain and preventing excess gestational weight gain in pregnancy	B	May 2021
Hepatitis B virus infection in adolescents and adults: screening: adolescents and adults at increased risk for infection	The USPSTF recommends screening for hepatitis B virus (HBV) infection in adolescents and adults at increased risk for infection. See the Practice Considerations section for a description of adolescents and adults at increased risk for infection	B	December 2020[a]

Hepatitis B virus infection in pregnant women: screening: pregnant women	The USPSTF recommends screening for hepatitis B virus (HBV) infection in pregnant women at their first prenatal visit	A	July 2019[a]
Hepatitis C virus infection in adolescents and adults: Sscreening: adults aged 18–79 years	The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18–79 years	B	March 2020[a]
Human immunodeficiency virus (HIV) infection: screening: adolescents and adults aged 15–65 years	The USPSTF recommends that clinicians screen for HIV infection in adolescents and adults aged 15–65 years. Younger adolescents and older adults who are at increased risk of infection should also be screened. See the Clinical Considerations section for more information about assessment of risk, screening intervals, and rescreening in pregnancy	A	June 2019[a]
Human immunodeficiency virus (HIV) infection: screening: pregnant persons	The USPSTF recommends that clinicians screen for HIV infection in all pregnant persons, including those who present in labor or at delivery whose HIV status is unknown	A	June 2019[a]

(continued)

Table 1.3 (continued)

Topic	Description	Grade	Release date of current recommendation
Hypertension in adults: screening: adults 18 years or older without known hypertension	The USPSTF recommends screening for hypertension in adults 18 years or older with office blood pressure measurement (OBPM). The USPSTF recommends obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment	A	April 2021[a]
Intimate partner violence, elder abuse, and abuse of vulnerable adults: screening: women of reproductive age	The USPSTF recommends that clinicians screen for intimate partner violence (IPV) in women of reproductive age and provide or refer women who screen positive to ongoing support services. See the Clinical Considerations section for more information on effective ongoing support services for IPV and for information on IPV in men	B	October 2018[a]
Latent tuberculosis infection: screening: asymptomatic adults at increased risk for infection	The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations at increased risk	B	September 2016[a]

Lung cancer: screening: adults aged 50–80 years who have a 20-pack-year smoking history and currently smoke or have quit within the past 15 years	The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 50–80 years who have a 20-pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery	B	March 2021[a]
Obesity in children and adolescents: screening: children and adolescents 6 years and older	The USPSTF recommends that clinicians screen for obesity in children and adolescents 6 years and older and offer or refer them to comprehensive, intensive behavioral interventions to promote improvements in weight status	B	June 2017[a]
Ocular prophylaxis for gonococcal ophthalmia neonatorum: preventive medication: newborns	The USPSTF recommends prophylactic ocular topical medication for all newborns to prevent gonococcal ophthalmia neonatorum	A	January 2019[a]

(continued)

Table 1.3 (continued)

Topic	Description	Grade	Release date of current recommendation
Osteoporosis to prevent fractures: screening: postmenopausal women younger than 65 years at increased risk of osteoporosis	The USPSTF recommends screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in postmenopausal women younger than 65 years who are at increased risk of osteoporosis, as determined by a formal clinical risk assessment tool. See the Clinical Considerations section for information on risk assessment.	B	June 2018[a]
Osteoporosis to prevent fractures: screening: women 65 years and older	The USPSTF recommends screening for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women 65 years and older	B	June 2018[a]
Perinatal depression: preventive interventions: pregnant and postpartum persons	The USPSTF recommends that clinicians provide or refer pregnant and postpartum persons who are at increased risk of perinatal depression to counseling interventions	B	February 2019
Prediabetes and type 2 diabetes: screening: asymptomatic adults aged 35–70 years who have overweight or obesity	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	August 2021[a]

Preeclampsia: screening: pregnant woman	The USPSTF recommends screening for preeclampsia in pregnant women with blood pressure measurements throughout pregnancy	B	April 2017[a]
Prevention of dental caries in children younger than 5 years: screening and interventions: children younger than 5 years	The USPSTF recommends that primary care clinicians prescribe oral fluoride supplementation starting at age 6 months for children whose water supply is deficient in fluoride	B	December 2021[a]
Prevention of dental caries in children younger than 5 years: screening and interventions: children younger than 5 years	The USPSTF recommends that primary care clinicians apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption	B	December 2021[a]
Prevention of human immunodeficiency virus (HIV) infection: preexposure prophylaxis: persons at high risk of HIV acquisition	The USPSTF recommends that clinicians offer preexposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at high risk of HIV acquisition. See the Clinical Considerations section for information about identification of persons at high risk and selection of effective antiretroviral therapy	A	June 2019

(continued)

Table 1.3 (continued)

Topic	Description	Grade	Release date of current recommendation
Rh(D) incompatibility: screening: pregnant women, during the first pregnancy-related care visit	The USPSTF strongly recommends Rh(D) blood typing and antibody testing for all pregnant women during their first visit for pregnancy-related care	A	February 2004[a]
Rh(D) incompatibility: screening: unsensitized Rh(D)-negative pregnant women	The USPSTF recommends repeated Rh(D) antibody testing for all unsensitized Rh(D)-negative women at 24–28 weeks' gestation, unless the biological father is known to be Rh(D)-negative	B	February 2004[a]
Sexually transmitted infections: behavioral counseling: sexually active adolescents and adults at increased risk	The USPSTF recommends behavioral counseling for all sexually active adolescents and for adults who are at increased risk for sexually transmitted infections (STIs). See the Practice Considerations section for more information on populations at increased risk for acquiring STIs	B	August 2020[a]
Skin cancer prevention: behavioral counseling: young adults, adolescents, children, and parents of young children	The USPSTF recommends counseling young adults, adolescents, children, and parents of young children about minimizing exposure to ultraviolet (UV) radiation for persons aged 6 months to 24 years with fair skin types to reduce their risk of skin cancer	B	March 2018[a]

Statin use for the primary prevention of cardiovascular disease in adults: Ppreventive medication: adults aged 40–75 years with no history of CVD, one or more CVD risk factors, and a calculated 10-year CVD event risk of 10% or greater	The USPSTF recommends that adults without a history of cardiovascular disease (CVD) (i.e., symptomatic coronary artery disease or ischemic stroke) 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 (i.e., dyslipidemia, diabetes, 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 for more information on lipids screening and the assessment of cardiovascular risk	B	November 2016[a]
Syphilis infection in nonpregnant adults and adolescents: screening: asymptomatic, nonpregnant adults and adolescents who are at increased risk for syphilis infection	The USPSTF recommends screening for syphilis infection in persons who are at increased risk for infection	A	June 2016[a]

(continued)

Table 1.3 (continued)

Topic	Description	Grade	Release date of current recommendation
Syphilis infection in pregnant women: screening: pregnant women	The USPSTF recommends early screening for syphilis infection in all pregnant women	A	September 2018[a]
Tobacco smoking cessation in adults, including pregnant persons: interventions: nonpregnant adults	The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and US Food and Drug Administration (FDA)-approved pharmacotherapy for cessation to nonpregnant adults who use tobacco	A	January 2021[a]
Tobacco smoking cessation in adults, including pregnant persons: interventions: pregnant persons	The USPSTF recommends that clinicians ask all pregnant persons about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant persons who use tobacco	A	January 2021[a]
Tobacco use in children and adolescents: Primary care interventions: school-aged children and adolescents who have not started to use tobacco	The USPSTF recommends that primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use among school-aged children and adolescents	B	April 2020[a]

Unhealthy alcohol use in adolescents and adults: screening and behavioral counseling interventions: adults 18 years or older, including pregnant women	The USPSTF recommends screening for unhealthy alcohol use in primary care settings in adults 18 years or older, including pregnant women, and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce unhealthy alcohol use	B	November 2018[a]
Unhealthy drug use: Sscreening: adults age 18 years or older	The USPSTF recommends screening by asking questions about unhealthy drug use in adults age 18 years or older. Screening should be implemented when services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred. (Screening refers to asking questions about unhealthy drug use, not testing biological specimens.)	B	June 2020
Vision in children ages 6 months to 5 years: screening: children aged 3–5 years	The USPSTF recommends vision screening at least once in all children aged 3–5 years to detect amblyopia or its risk factors	B	September 2017[a]

(continued)

Table 1.3 (continued)

Topic	Description	Grade	Release date of current recommendation
Weight loss to prevent obesity-related morbidity and mortality in adults: behavioral interventions: adults	The USPSTF recommends that clinicians offer or refer adults with a body mass index (BMI) of 30 or higher (calculated as weight in kilograms divided by height in meters squared) to intensive, multicomponent behavioral interventions	B	September 2018[a]

[a] Previous recommendation was an "A" or "B"

Table 1.4 USPTF grade definitions [10]

Grade	Definition	Suggestions for practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial	Offer or provide this service
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial	Offer or provide this service
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small	Offer or provide this service for selected patients depending on individual circumstances
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits	Discourage the use of this service
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined	Read the clinical considerations section of UPSTF recommendation statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms

encourage conversations about issues that are very relevant to a patient's health and the care delivered. This approach yields a better understanding of the individual patient and allows for thoughtful accounting of impact that may be driven by social determinants, behavioral health, substance use, and other health behaviors.

The use of evidence-based screening tools in this realm has increasingly become the standard. The standardization of behavioral health (depression, anxiety) and substance use (alcohol, drugs, and tobacco) screenings has been well studied [13, 14]. In efforts to better understand the "whole patient," the clinician can take active steps in aligning screening strategies with focused examinations and additional testing, toward the maintenance of overall health.

Effective communication is a key factor in discussing screening tools/exams with patients to provide unbiased information on both the benefits and the harms of screening and to demonstrate a respect for autonomy [15, 16]. The conscious act of normalizing the use of screening tests and assessments is critical when discussing the risks, benefits, and potential results that may be associated. Though part of everyday routine for the average clinician, for the patient, a screening test/assessment can be a cause for added stress and uneasiness and can affect the relationship. Normalizing the process and transparently explaining to patients the reason behind certain assessments (alcohol/drug use assessments, depression screening, etc.) can prevent feelings of embarrassment and shame. Skillful communication can prevent the patient from becoming defensive or feeling singled out and will hopefully open the door for sharing of important information. Simple approaches, like "I am going to ask you a few questions that I ask of all my patients" or "Based on what we have been discussing and the physical exam, I recommend that we send you for a chest X-ray and possibly a CT scan," can help address/alleviate potential stigma and assumptions and help clarify why certain testing is suggested [17, 18]. Of note, lab tests and imaging, where results will not be commu-

nicated during the initial appointment, require clear explanation on how and when (1) results and (2) next steps will be communicated. This is relevant in the context of wide use of patient portals where patients will likely view both results and lab/radiology interpretation before their clinician does [19, 20].

Best practices when communicating with patients guide clinicians to start with open-ended questions and then narrow the focus with close-ended questions. Similarly, different degrees of screening can be utilized as clinical decision support tools. Starting off with a broad screening process (one with high sensitivity and low specificity, yielding increased false positives) will allow the clinical team to gauge if there is a need to further investigate. A screening tool that can better hone in on a relevant issue (ideally, a process with a high sensitivity and a high specificity, yielding decreased false positives) can be used in a secondary manner if necessary. A clinical example of this concept is the process used for screening for substance use. Through the process known as screening, brief intervention, and referral to treatment (SBIRT) for substance use [21, 22], a prescreening is completed. If the patient screens positively with the prescreening tool, a follow-up screening is conducted which will further identify a patient who is using alcohol beyond the healthy drinking guidelines, potentially increasing the risk for health and psychosocial consequences [23].

It is important to highlight that screening guidelines, protocols, and processes are ever evolving based on clinical research investigating benefits vs. risks and patient feedback. Over the years, certain screenings have triggered controversial debates based on review of mortality and morbidity rates related to screening. Certain screenings may yield an increased number of false positives, leading to further invasive investigations that can increase the degree of risk to patients. Identifying patients at risk of overmedicalization may be referred to as *quaternary prevention* [24].

One example is the prostate-specific antigen (PSA) blood test for detection of prostate cancer. As of 2018, PSA testing has been listed as a grade "C" for men aged 55–69 and grade "D" for those aged 70+ years old [25]. Multiple clinical trials have shown evidence that a substantial percentage of men who have asymptomatic cancer detected by PSA screening have a tumor that either will not progress or will progress so slowly that it would have remained asymptomatic for the man's lifetime (i.e., "overdiagnosis" or "pseudo-disease") [26]. Subsequent biopsies for positive PSA testing have led to a multitude of complications (pain, discomfort, bleeding, psychological harm from false-positive results, etc.), and certain studies even recommend that if PSA testing is to continue, the threshold triggering biopsy or need for treatment should be increased [27, 28]. The evolution of this discussion and research has deemed that the benefits of PSA testing may not outweigh the harms.

Conversely, there has been a paradigm shift in the thinking and evidence around alcohol use screening, moving from the CAGE to the AUDIT questionnaire [29]. Historically, the CAGE, a tool with high specificity (low false positive rate), was the standard screen used to detect lifetime alcohol abuse and/or dependence [30], yet it failed to optimally identify current heavy drinking [31]. Based on current research, alcohol screenings which tend to have a higher false positive rate, such as the AUDIT, have been received differently. There is more comfort with the false positives resulting from these screenings versus that of the PSA screening due to the lack of potential downstream harm (i.e., invasive confirmatory tests, psychological distress, etc.). The research in this realm has led to a change in the guidelines recommending the use of evidence-based tools to standardize screening protocols which will more likely detect risky use of substances, not just dependence and substance use disorders.

Clinicians should both understand for themselves and be able to explain to their patients that no screening test is 100% sensitive or specific. Screening tools should be used to supplement physical exam and clinical judgement, but not replace them [32].

Physical Exam

While the concept of the comprehensive physical exam in practice remains controversial [33, 34], few could dispute the value it holds as an opportunity to discover vital clues to diagnose [35] and build trust and rapport with a patient [36, 37]. The physical exam is a skillful art form that with time and experience clinicians can master. This is an iterative process where knowledge, coupled with experience, yields the ability to conduct the appropriate and focused physical exams.

The approach toward a physical exam includes consideration of patient particulars (i.e., age, gender, disposition, personal risk factors, family history, etc.) in addition to the historical account of a patient's overall health and psychosocial status, as well as their presenting concerns. Additionally, taking account of the expectations and perceptions of a patient [38, 39] can influence the use of physical examinations in a clinical visit. Placing a stethoscope on a patient's chest and palpation of one's abdomen can satisfy the expectations of a patient and lead to improved trust [40–42].

Examinations can be comprehensive "head to toe," systematically following the review of systems and/or more focused and based on the presenting complaint. The physical exam can be employed for screening, investigation, and/or for confirmation of diagnostic possibilities; however, with the rapidly evolved utilization of telehealth, driven by response to the coronavirus disease-19 (COVID-19) pandemic, the element of touch was significantly challenged, and at times, removed.

Telehealth has become an essential component of providing care. This medium is especially useful when people are in quarantine or regulations limit in-person interactions and enables patients, in real-time, through contact with a healthcare provider, to seek advice and care for their health problems [43].

The use of virtual visits requires physicians to think proactively about what information they wish to obtain from the examination that can be performed remotely. While video

can provide visual clues that one may also obtain on an in-person examination, it is possible to elicit additional valuable clinical information through various patient-assisted maneuvers [44]. When feasible, obtaining a baseline in-person exam and setting expectations prior to beginning virtual encounters should improve diagnostic accuracy [45].

Vaccinations

The Centers for Disease Control and Prevention (CDC) recommends vaccinations from birth through adulthood to provide a lifetime of immunity [46] and that all adults need immunizations to help them prevent acquiring and transmitting serious diseases that could result in poor health, missed work, medical bills, and not being able to care for their family [47]. In contrast to the pediatric and adolescent vaccination recommendations and schedule, adult vaccinations are typically focused toward at-risk populations and those in certain occupations. Despite efforts to raise awareness about how vaccinations help reduce the prevalence of diseases (e.g., COVID-19 [48], influenza, human papillomavirus (HPV) [49], pertussis, pneumococcal disease, etc.), vaccination compliance remains low [50, 51].

Similar to the communication strategies utilized when normalizing screening, discussion of results, or elements of a physical exam, there needs to be an active effort to discuss vaccinations. Physician and consumer surveys conducted by the National Foundation for Infectious Disease (NFID) highlight communication breakdowns between doctor and patient, leaving many adults unaware of the need for vaccines [47].

In December of 2020, an updated version of the Advisory Committee on Immunization Practices (ACIP) vaccination table was approved (Table 1.5) [52, 53]. It is vital for clinicians to be very familiar with this guidance as it details vaccines routinely recommended for adults, contains important footnotes for each vaccine, and highlights the primary contraindications and precautions for commonly used vaccines [54].

Table 1.5 Recommended adult immunization schedule for ages 19 years or older, United States, 2021 [52]

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV4)	[a]	1 dose annually[a]	[a]	[a]
or	[a]	or	[b]	[b]
Influenza live attenuated (LAIV4)		1 dose annually[a]		
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes[c])[d]			
	1 dose Tdap and then Td or Tdap booster every 10 years[a]			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)[a]			[b]
Varicella (VAR)	2 doses (if born in 1980 or later)[a]	[a] [d] 2 doses[d]		
Zoster recombinant (RZV)	[b]	[b]	2 doses[a]	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition[a]	27 through 45 years[e] [e] [b]	[b]	[b]

(continued)

Table 1.5 (continued)

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Pneumococcal conjugate (PCV13)	1 dose[d]			[d] 1 dose[e]
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication[d]			1 dose[a]
Hepatitis A (HepA)	2 or 3 doses depending on vaccine[d]			
Hepatitis B (HepB)	2 or 3 doses depending on vaccine[d]			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes[c] for booster recommendations[d]			

Meningococcal B (MenB)	[d]	2 or 3 doses depending on vaccine and indication, see notes[c] for booster recommendations[d]
	19 through 23 years[e]	[d] [d]
Haemophilus influenzae type b (Hib)	1 or 3 doses depending on indication[d]	

Administer recommended vaccines if vaccination history is incomplete or unknown. Do not restart or add doses to vaccine series if there are extended intervals between doses. The use of trade names is for identification purposes only and does not imply endorsement by the ACIP or CDC

[a] Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

[b] No recommendation/Not applicable

[c] See notes by visiting https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-compliant.html

[d] Recommended vaccination for adults with an additional risk factor or another indication

[e] Recommended vaccination based on shared clinical decision-making

Additionally, to assist physicians and patients with their understanding of which vaccinations are relevant to care, the CDC site has a user-friendly "Vaccine Quiz" available [55].

Health Maintenance

The primary care clinician follows their patient throughout their medical journey, building a partnership to collaboratively discuss, plan for, and achieve one's optimal health. The interaction between the clinician and patient serves as a springboard to motivate sustainable decisions the patient will need to maintain.

Telehealth has added value to the continuum of care; however it is not the only major aspect that has changed the paradigm of healthcare due to COVID-19. Traditional "sick visits" have relocated from primary care to urgent care, and the reduction of primary care touchpoints impacts a primary care clinician's ability to appreciate the complete picture of an individual's health [56, 57]. To account for this and to bridge the gap, it is important to ask about other healthcare utilization outside of the primary care practice [56, 57].

Capitalizing on the rapport, trust, and partnership built, clinicians can focus efforts on clearly and transparently discussing the patient's health and goals for care. Using evidence-based guidelines like the USPSTF gives the clinician the power and the knowledge to help guide the conversation as well as the overall care of the patient throughout the continuum, striving for optimal health in the physical as well as psychosocial domains.

Clinical Pearls

- Some screening tests and examinations can be sensitive in nature and embarrassing to the patient.
- Effective communication and normalization can help reduce avoidance on the patients' and clinicians' part.
- Evidence-based guidelines assist the clinician to focus encounters and help guide interventions.

Don't Miss This!

- Excellent evidence exists to help guide clinical care—use it to identify important clinical concerns as well as to avoid testing that may lead to unnecessary cost and risk to the patient with little known benefit.
- Become familiar with tools used to screen for behavioral health issues and substance use. Comfortable use by the provider will help build trust and partnership and will encourage the patient to respond openly.
- Learning how to focus the physical exam based on the patient's demographics, history, and their presenting concerns is critical to effective encounters in the clinical setting.
- When using telehealth, it is possible to elicit additional valuable clinical information through various patient-assisted maneuvers.

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Chapter 2
Covid-19 for the Primary Care Clinician: Current Recommendations—Don't Blink!

Matthew Love

Introduction

Writing a chapter about Covid-19 for inclusion in a hardcopy book is a fool's errand. Already, in the course of the 2-plus years of the pandemic, diagnostics and therapeutics and preventive strategies have undergone wholesale changes. Even the presenting symptoms and signs of the disease have changed within the last year. What's safe to say is that the virus *will* evolve [1]. So this chapter will not include information about Wuhan and alpha and delta variants of the virus that is no longer relevant to current practice. More so than with any other known disease, you must keep abreast of current recommendations of the CDC and your state and city health departments. Knowing the local status of the epidemic will affect the assessment of symptoms, the interpretation of diagnostic tests, and the choice of treatment for many of the individual patients you see.

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Covid-19 illness typically has several phases. The pre-symptomatic phase occurs a few days after exposure. Viral replication in the upper respiratory tract may have reached a point such that the patient feels nothing but harbors a viral load sufficient to render him contagious. In the next phase, the viral load increases exponentially, and symptoms appear. The virus circulates widely in the body, replicating in the lower respiratory tract, the brain, the blood, adipose tissue, and other organs. In the next phase, typically beginning several days after symptom onset, a massive inflammatory response contributes to the multisystem devastation caused by the virus. Usually by day 10 of symptoms, the immune system has nearly cleared the virus from the body. In the convalescent phase, lasting several weeks, the body usually heals and recuperates fully. However, a significant percentage of patients suffers persistent symptoms and apparently permanent damage—most commonly called long covid. Vaccination, antiviral treatment, passive antibody infusion, and other treatments alter the arc of disease, and individual patients often deviate from the typical course. Indeed, most people infected with the Sars-CoV-2 virus do not develop Covid-19.

Below, I confine my discussion to the areas encountered in the outpatient practice setting, not the emergency room or the inpatient service.

Symptoms

The symptoms of Covid-19 were well known to all—fever, cough, myalgia, and headache were the most common; rhinorrhea and gastrointestinal symptoms were also quite common; dyspnea, the most dreaded, was common too [2]; loss of smell and taste were almost pathognomonic. But then, in early December 2021, I saw three patients in a row in walk-in clinic complaining of sore throat without any other symptoms. All were elderly with underlying conditions, but they looked fine, and their throats looked normal. They did not have much in support of a diagnosis of Covid-19—and were

it not for the drumbeat of Omicron warnings coming from the CDC and a comment on a WhatsApp group chat that included European physicians about the unusual frequency of sore throat as a single symptom, I might have foregone Covid-19 testing.

As of this moment, with Omicron being the major extant variant—cough, sore throat, and rhinorrhea are now the top three symptoms [3, 4]. The others listed above still occur, though loss of taste and smell is much less common now.

It should be noted that, especially for Omicron, asymptomatic infection is probably the most common "presentation" of all.

Other History

The risk factors for severe Covid-19—obesity, immunosuppression, cardiopulmonary disease, diabetes, advanced age, and vaccination status—are well known and should be ascertained for each patient. These are detailed in the Treatment section below. The patient's exposure risk should also be reviewed. Patients often underestimate their risk or fail to identify obvious exposures. The patient may trumpet their caution—they never leave the house, they only meet their friends outdoors—but fail to mention that their home health aide is coming into their small apartment daily, after traveling on the bus or that their son, who lives with them, is going to work every day. While the FDA-authorized vaccines have not been effective at preventing mild/moderate upper respiratory infection, they have proven very effective at preventing infection severe enough to require hospitalization.

Physical Exam

Vital signs should be taken carefully. The most ominous finding is a low oxygen saturation. Anything in the high 90s is reassuring. Patients with resting saturations in the mid-90s should be made to ambulate for a couple of minutes to see if

they desaturate. (Desaturation, even in patients who are obese or deconditioned, is not normal.) Patients with resting saturations in the low 90s (unless this is their baseline) should be referred for admission. Hypoxemia often worsens quickly and dramatically. The HEENT exam is often normal—the rhinorrhea is not usually profuse, and the Covid-19-infected throat usually does not show any exudate or erythema. Any abnormal finding on lung exam warrants a CXR. The extremities should be checked for swelling, bearing in mind that Covid-19 is a hypercoagulable state—DVTs and PEs are frequent.

Lab Tests

The patient should be tested for Covid-19 if they haven't been tested yet. Which test to use will depend on test availability, the circumstances of the testing situation, the rapidity of the turnaround, the season of the year, and the particulars of the Covid-19 variant. For the purposes of this chapter, I will assume that the testing circumstance is the evaluation of a recently symptomatic patient. There are two kinds of tests which are widely available. The polymerase chain reaction (PCR), which copies and amplifies minute amounts of viral RNA to make it detectable, has accurately and sensitively diagnosed all known Covid-19 variants to date. "Rapid PCR" tests, with results available in 1–2 h, are available but have been in short supply during the pandemic waves. Rapid antigen tests are immunoassays that detect the presence of specific viral antigens typically within 15–30 min.

Figure 2.1 [5] illustrates the usual timeline of infection and test results. In the pre-symptomatic period, the PCR (called an RNA test in the figure), with its amplification of RNA, may be positive. The rapid antigen test only becomes positive when there is a higher viral load in the sample, usually right around the time symptoms appear. After several days when both are positive, the patient's immune system catches up and antibody production (first IgM and then IgG) increases and viral load decreases. At a certain point (about 5 days after

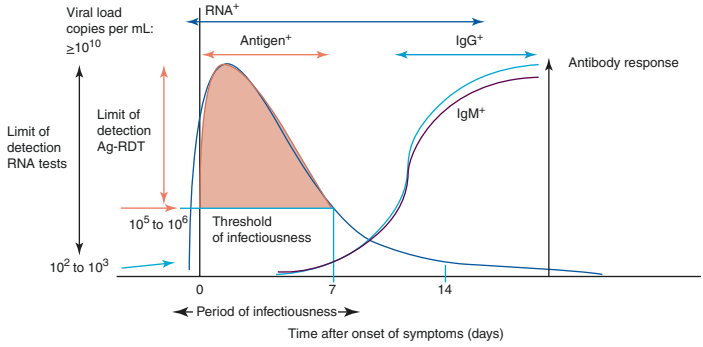

FIGURE 2.1 PCR/RAPID Ag detection

Omicron symptom onset or first positive test), the viral load will decrease sufficiently that the patient is no longer infectious. The PCR will continue to be positive—the test will amplify the relatively few whole viral particles remaining as well as the blasted bits of viral RNA in the mucosa—while the rapid antigen will turn negative, more accurately reflecting the infectivity of the patient. (This is why, early on in the pandemic, health departments stopped requiring negative tests to end isolation in non-immunocompromised patients. Instead, pre-specified isolation periods were designated.)

If the patient is a candidate for interruptive/abortive therapy (see below), a rapid test, either rapid PCR or rapid antigen, must be used so that the patient can obtain the medication in a timely manner. Although there are approved fast PCRs with results available in an hour, these have been hard to obtain in previous waves, so a rapid antigen test—an immunoassay that detects the presence of a specific viral antigen—is the next best choice. In the setting of an epidemic wave of infection, the false negative rate of the rapid antigen test is quite low, and a positive rapid test can be considered sufficient to initiate treatment.

If the patient is not a candidate for interruptive/abortive therapy, a regular PCR will be the most useful, presuming a reasonable turnaround time. The PCR will be positive even when the viral load is low, enabling accurate targeting of isolation and quarantining advice.

PCRs are now available that simultaneously test for influenza and RSV. All other things being equal, these will be helpful in some cases.

For mildly symptomatic patients, laboratory tests beyond the Covid-19 test itself are not particularly helpful. The decision about whether to send the patient home or refer the patient to the ER can be made based on the history and physical alone. In elderly patients, a CBC and chemistry may help to identify conditions lower down on the differential diagnosis—such as hyponatremia, hyperglycemia, or bacterial infection.

Differential Diagnosis

There is so much overlap in symptoms with other respiratory infections like influenza that no symptom or symptom complex is distinct enough to be pathognomonic. The most important variable in assessing whether a particular patient is more likely or less likely to have Covid-19 is the status of the epidemic in your local area. When the wave is crashing upon your local shores and the prevalence is high, almost every patient with an upper respiratory symptom or a sore throat and most patients with diarrhea, pneumonia, altered mental status, chest pain, or syncope will have Covid-19. Conversely, when the prevalence is low, a large majority of patients with these symptoms will not have Covid-19. During the latest Omicron wave of the pandemic (when the estimated prevalence of the coronavirus infection was 50% of the New York City population), one challenge was making sure to *not* attribute everything to Covid-19. The usual background frequencies of bacterial pneumonia, enteritis, strokes, and heart attacks were unchanged. Indeed, there were far fewer patients hospitalized with symptomatic Covid-19 than there were patients hospitalized with incidental Covid-19—i.e., patients admitted for trauma, cholecystitis, strokes, heart attacks, and other problems who happened to test positive for Covid-19.

Treatment

An important task for the outpatient practitioner is identifying those patients at high risk for progression from upper respiratory disease to lower respiratory disease. The ability to interrupt or mitigate this progression promises to become an important weapon in the clinician's armamentarium. If initial efficacy estimates are borne out, treating patients at high risk with the antiviral pill Paxlovid will be more efficacious than the treatment of the disease once the lower respiratory tract has become involved. Paxlovid is nirmatrelvir, an inhibitor of the SARS-CoV-2-3CL protease, an enzyme that the virus needs to replicate, co-administered with a low dose of another protease inhibitor, ritonavir, to slow down the metabolism of the active drug.

In the randomized, placebo-controlled trial of over 2000 patients at high risk for progression to severe Covid-19 submitted by Pfizer to obtain its Emergency Use Authorization from the FDA, Paxlovid, a protease inhibitor which blocks viral replication, was 89% effective at preventing hospitalization and 100% effective at preventing death in a randomized, placebo-controlled trial of over 2000 patients at high risk for progression [6]. As of April, 2022, the criteria for prescribing Paxlovid (or the less impressive Molnupiravir [7]) are a positive test, mild-to-moderate symptoms, symptom duration of 5 days or less, and a high risk of progression to severe Covid-19. The co-morbidities conveying the higher risk are as follows:

- Age 65 or older
- Body mass index (BMI) >25
- Chronic kidney disease
- Diabetes
- Immunocompromising conditions or currently receiving immunosuppressive treatment
- Pregnancy
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (e.g., chronic obstructive pulmonary disease, asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension)

- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation (not related to Covid-19)
- Incomplete vaccination

These criteria have changed along with the availability of the medication. For example, the qualifying BMI in New York State has dropped from 30 to 25 as more pills became available. It is also important to keep in mind that while the clinical trials conducted by the pharmaceutical manufacturers were sufficient to warrant Emergency Use Authorization by the FDA, the medicines have not been sufficiently vetted to gain full approval. The range, severity, and frequency of adverse reactions to the medicine when in wide clinical use are not yet known. In a patient with a high risk of severe Covid-19, the benefits of treatment outweigh the unknown risk. But the risk/benefit ratio in lower risk patients is much murkier and awaits clarification through further study. The medicine cannot be given to patients with GFR < 30 or severe liver failure and must be dose-adjusted for GFR < 60.

Another possible option for the higher-risk patient if Paxlovid is unavailable is immediate referral for the infusion of Covid-19-specific anti-spike protein antibody cocktails. The window for referral is slightly wider—7 days from symptom onset (as opposed to 5 for the antivirals). But the existing antibody products may not be effective against the next variant of the SARS-CoV-2. For example, two of the three products that were developed for the delta variant were found to be ineffective against Omicron only after thousands of infusions were performed. All three are ineffective against the current Omicron BA.2 subvariant, though a newly released product, bebtelovimab, appears to be effective. Another antiviral, Molnupiravir, which was less effective in the initial

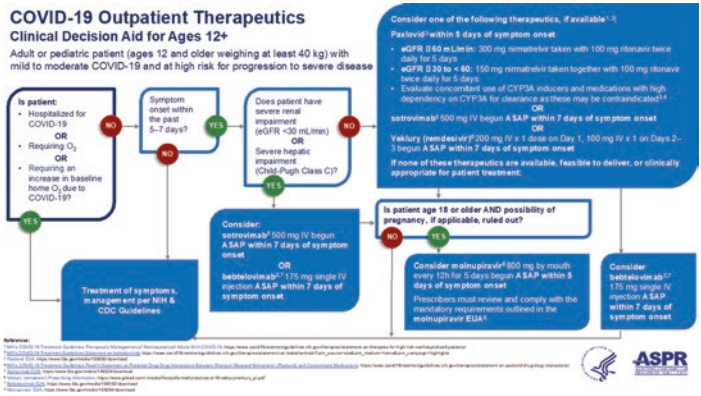

FIGURE 2.2 Algorithm for Covid-19 outpatient therapeutics

study, may also be considered if the other options are not available. Again, staying current is crucial.

In sum, all patients being evaluated for possible Covid-19 should be seen with an eye toward prescribing either a protease inhibitor or an antibody to prevent progression to severe disease. See Fig. 2.2 for an algorithm to guide decision-making. (Note that already the antibody recommendations are out of date.)

Patients who have a positive test or are awaiting test results should be advised to isolate themselves as much as possible for the time period required by the local health department. If they live with others, especially high-risk individuals, they should be given the option of checking into a Covid-19 hotel or other isolation facility if available. The home is one of the main sites of transmission [8], and in the Covid-19 hotel, the patient can be observed and transferred promptly to a hospital if he or she deteriorates clinically. If the patient is being sent home without admission, close follow-up especially for high-risk patients is warranted. It is difficult to know where the patient is in the course of their illness. A newly symptomatic patient may be toward the beginning of their illness, just exiting the early asymptomatic period. While one doesn't want to fill the hospital beds with patients who don't currently

require treatment, one is loath to send a patient home when there is a significant probability that they will worsen and require admission later. The patient who is sent home to isolate, particularly if they live alone, may be understandably fearful. Besides the Covid-19 hotel, two other follow-up options have been piloted. In England, patients discharged to home were given home pulse oximeters and enrolled in a "virtual ward," where hundreds of patients had remote access to a healthcare practitioner 24 h a day who was assigned to monitor them and advise them about self-care and to transfer them to the hospital when necessary [9]. This arrangement may have significantly reduced mortality. In another study, a more common arrangement—providing the patient with pulse oximetry and instructions to come to the Emergency Room if the oxygen saturation dipped below 92% at rest—found that with the 92% cutoff, patients who came to the hospital were there in time to initiate treatment for acute Covid-19 and that 33% of the enrollees who did not come to the hospital would've done so if they didn't have the oximeter [10]. Another arrangement that was tried many places was sending automated text messages to patients—were they improving, staying the same, or getting worse? Those who were getting worse were contacted.

Prevention

It almost goes without saying that, for Covid-19, an ounce of prevention is worth a pound of cure. The approved vaccines save lives. Masks, especially high-quality, medical-grade masks, save lives and are now widely available for free from local pharmacies.

Long Covid

After the first wave of the pandemic subsided in late spring of 2020, it became apparent that long after Covid-19 tests had turned negative, lab values had returned to normal, and

patients had been discharged from the hospital, a huge number of them were not bouncing back to normal. Even allowing for extended convalescence and permanent damage from the acute illness, a puzzling myriad of symptoms persisted. Initially, reports were confined to patients who had been hospitalized with Covid-19, but it soon became apparent that many patients with persistent and sometimes worsening symptoms had had only moderate or even mild acute illness. Prevalence estimates for this syndrome varied wildly, depending on the method of ascertainment, the study population, and the case definition used – but even the most conservative estimates put the number of patients suffering from long Covid-19 in the millions.

The syndrome has been variously dubbed long covid, post-acute sequelae of Covid-19, or simply post-Covid-19 condition. The World Health Organization definition is generally accepted: "Post Covid-19 condition occurs in individuals with a history of probable or confirmed SARSCoV-2 infection, usually 3 months from the onset of Covid-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis." The most common symptoms are persistent generalized fatigue [11], dyspnea, and cognitive difficulties or "brain fog." These range in severity from bothersome to severely disabling. Other post-Covid-19 symptoms include headaches, joint pain, tachycardia, chest pain, hair loss, myalgia, dysgeusia, dysosmia, and insomnia. Of particular note is the high prevalence of persistent—or new—psychiatric symptoms [12]. Many studies have shown that these post-Covid-19 sequelae occur not only in those patients who've had severe Covid-19, but in those with moderate or mild disease as well [13].

All symptoms should be thoroughly evaluated to rule out other conditions and to help gauge the severity. If the patient does not have a documented positive Covid-19 test, previous infection can be demonstrated with a Covid-19 antibody test (either total Covid-19 antibodies or IgG). Lab tests usually return to normal in a few weeks. Chest X-ray infiltrates usually clear up in a few months. If the patient has plateaued or

clinical improvement is slow, advanced testing and specialty consultation should be initiated even though the 3-month mark may not have been reached.

One frequent presentation seen weeks after moderate-to-severe Covid-19 pneumonia is persistent oxygen desaturation with minimal exercise accompanied by tachycardia. Usually, labs and images are normal or improving; echo is normal; and PFTs may show some restriction and diminished diffusing capacity, but not to a degree that accounts for the symptoms. There is a high prevalence of postural orthostatic tachycardia syndrome (POTS) in post-Covid-19 patients [14]. Vitals should be checked standing and supine. Even if there is no dramatic change in blood pressure and pulse, discontinuation of antihypertensives should be attempted, and salt intake and hydration should be encouraged. Compression stockings may also be of benefit. If available, invasive cardiopulmonary exercise testing should be ordered—impaired peripheral oxygen extraction is an intriguing finding in an initial study that explains a lot [15].

Hypotheses as to the pathogenesis of post-Covid-19 condition abound, but there are as yet only intriguing clues. The NIH has funded a huge study with the aim of elucidating the pathogenesis of long covid. Hopefully, the knowledge gained from the study will lead to effective treatments and shed light on other medically unexplained illness like chronic fatigue syndrome and fibromyalgia.

There are currently no specific treatments for long covid. Treatment is symptom-based. The patient should be referred to a physiatrist early on to begin the arduous work of rehabilitation. There are many centers with specific Covid-19 programs; if available, the patient should be directed to one of these.

There are three Covid-19 vaccines approved for use in the United States. See Table 1, 2, 3 for the Covid-19 vaccine series schedule for 6 months and older [16]. The Pfizer/BioNTech and Moderna vaccines are both mRNA vaccines. Lipid nanoparticles carrying the mRNA of the coronavirus spike

protein (the only viral protein "visible" to the immune system) fuse with skeletal myocyte membranes and gain entry into the cytoplasm. The mRNA is translated by the ribosomes, leading to the production of the viral spike protein, which migrates to the cell membrane where it triggers the immune response. The Janssen vaccine is a viral vector vaccine. DNA instructions for making the spike protein are embedded in adenovirus particles which have been modified to be replication-incompetent. The adenovirus particles carry the spike-protein DNA into cells, where translation, production, and presentation of the protein ensues [17].

Clinical Pearls

- Have a low index of suspicion for testing, especially with high-risk patients.
- Current Covid-19 variants (2022) do not usually present with loss of smell and do not usually cause pneumonia.
- Test early and treat early especially those at high risk of progression.
- Remain up-to-date on national and local guidelines for treatment and vaccination/boosters

Don't Miss This!

- Covid-19 can present with only one symptom, like sore throat.
- Any patient with dyspnea needs to be evaluated in person, and pulse oximetry should be tested.

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Chapter 3
Transition Care of Teens with Chronic Health Conditions

Catherine Waymel and Kamala Gullapalli Cotts

Introduction

Transition is the "purposeful, planned movement of adolescents and young adults (AYA) with chronic physical and medical conditions from child-centered to adult-oriented healthcare systems" [1]. At least 30% of young adults have one or more chronic conditions, and as of 2016 approximately 6% of those younger than age 17 have disabilities [2, 3].

In 2011, the American Association of Pediatrics (AAP), American Association of Family Practitioners (AAFP), and the American College of Physicians (ACP) released a clinical report [4] containing guidelines to aid pediatricians, family practitioners, and internists in the transition of care of the adolescent (Table 3.1). In this report, special focus was given to caring for those with special needs and outlined the impor-

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Table 3.1 Six core elements of transition for adult providers

Age	Transition step
12–14	Transition healthcare policy statement • Create and discuss with young adult/guardian
14–17	Tracking and monitoring • Track young adult's progress to increase knowledge of health and adult healthcare system Transition readiness and goal-setting • Discuss strategies for orientation to adult practice
17–18	Written healthcare plan • Update plan to include required additional skills
18–21	Transfer of care/initial visit • Self-care assessment
3–6 months after transition	Transition completion/continuity of care with adult provider • Continue building self-care skills

tance of beginning transition-related conversations early, and creating a specific plan with the patient's family with focus on medical care, insurance issues, and community support. A successful transition to an adult healthcare provider occurs when adolescents and young adults gain skills and support needed to successfully manage their health.

Barriers in Transition Care

Barriers for adolescents and young adults with special health care needs (AYASHCN) stem from factors relating back to the patient, the provider, and community at large. Patients themselves are often initially unequipped to advocate for their own needs because there is relatively high parental involvement in the care of childhood chronic disease. This leads to lapses in the development of self-management skills, as youth tend to defer

medical decision-making to their parents and rely on their parents for basics of health maintenance such as making doctor's appointments and administering medication [5]. Another barrier is lapse in insurance that many young adults experience in the transition process. In one 2008 study [6] of low-income young adults who aged out of a public program for children with special healthcare needs (CSHCN), 40% had a gap in insurance coverage after reaching age 21. Overall, 65% reported at least one adverse transition event affecting access to care. Recent healthcare policy allows for young adults to remain insured under their guardian's insurance plans until their mid-20s. Despite this, insurance gaps and delayed care are prevalent among these low-income young adults.

Patient and Family Perspectives

Overall, many patients and their families feel unprepared for the transition process and are hesitant to develop a therapeutic relationship with a new provider [7]. Pediatric care is multidisciplinary and family-centered in individuals with chronic health conditions, leading to strong outcomes in both the inpatient and outpatient setting [8]. Adult care tends to be more focused on autonomy and patient motivation. However, children with chronic diseases have varying levels of self-advocacy skills and will usually have caretakers present for their appointments, and providers must accommodate for this change in visit dynamics.

Regarding family involvement, several studies indicated that while caregivers are concerned that young adult patients cannot independently manage their own health [9, 10], many young adult patients self-report being ready for this responsibility [10]. Caregivers are also concerned that adult healthcare providers do not want their involvement [11]. In general, families and case managers expressed concerns about physicians' attitudes, ability to handle ordinary and extraordinary health maintenance, and ability to refer appropriately. There were additional concerns regarding the appropriateness of specialty and emergency services [5].

Provider Perspectives

Primary care providers in internal medicine face many challenges in caring for AYASHCN. As survival rates and life expectancy of these individuals increase, these disorders are becoming more common in the adult population, and adult providers are inheriting a population of patients with conditions for which they may have had limited training. Several studies have shown that there is a paucity of adult subspecialty services for AYA patients with childhood-onset conditions [11, 12]. A survey of internists [13] highlighted the lack of adult subspecialists to share in the care for patients with congenital and childhood-onset disorders. This survey [13] explored internists' interpersonal concerns and stressors with caring for AYASHCN. It revealed that internists agree with caregivers regarding patient readiness to make independent decisions, are concerned that families will not stay involved when needed (especially for patients with intellectual disability or cerebral palsy), and can be challenged by families' expectations regarding length of visits with internists. Additionally, internists had concerns about the need to face disability and end-of-life issues both at an early age and early in the doctor-patient relationship. Finally, the survey revealed that internists experienced financial stress and time pressure associated with the care of this complex patient population. Provisions for billing highly complex visits are often not clearly delineated for patients who suffer from chronic disease, often resulting in poor reimbursement for additional time spent with patients.

Many internists reported that they feel uncomfortable providing primary care for young adults with childhood chronic diseases [14]. Since there are no set guidelines on transitioning children with chronic disease, internists may inherit patients merely because the patient has reached a certain age, instead of other developmental indicators such as competence and milestones [15, 16]. Pediatricians, often left without clear guidance on creating portable medical summaries, are challenged with summarizing two decades of medical

history, and poor transfer of healthcare information can lead to delays in receiving adult-oriented care [17]. Internists, often not having received a portable health summary, must generate complex histories in the limited time of an initial patient encounter.

Transition resources published by AAP, and Got Transition, can help address some of these barriers by providing resources to healthcare professionals, patients, and their families. The ACP Council on Subspecialty Societies (CSS) partnered with Got Transition [18] and formed specialty society workgroups to improve internists' ability to care for young adults with congenital or childhood-onset conditions. These new condition-specific transition tools are available for general and subspecialty practices caring for transitioning patients [4].

Initial Evaluation of Teens with Chronic Health Conditions Transitioning to Adult Providers

Portable Medical Summary

The American Association of Pediatrics recommends that each AYA preparing to transition should work with his or her pediatricians and families/guardians to generate a portable medical summary that outlines the patient's medical history [4]. This document should be shared with the patient and any future providers. Internists should be granted access to this document before the encounter to become familiar with the patient's condition and the potential complications.

Assessment of Functional Status

The initial visit with an adult provider should include an assessment of functional status for patients with chronic diseases of childhood, as individuals with chronic childhood

conditions may or may not have a developmental disability or an intellectual disability. A developmental disability (DD) is a severe, chronic disability that is attributable to a mental or physical impairment or a combination and begins prior to the age of 22. To qualify as developmentally disabled, substantial functional limitations must be documented in three or more areas of major life activity, such as self-care, receptive and expressive language, learning, mobility, capacity for independent living, and economic self-sufficiency [19]. Currently, over six million individuals in the USA have developmental disabilities [20]. A subset of patients with developmental disabilities also has an intellectual disability (ID). The prevalence of ID is estimated at approximately 1% of the population in the USA and Western European countries [21, 22]. The American Association on Intellectual and Developmental Disabilities (AAIDD) defines ID as both an IQ score below the range of 70–75 (two standard deviations below the mean) and limitations in adaptive skill areas that originate prior to age 18 years [23]. The limitations are described as conceptual, social, and practical deficits (Table 3.2); the definition requires that individuals test at least two standard deviations below the mean in one or in combination of all three adaptive skill areas.

A practical approach to assess the patient's functional status during the initial visit is to assess the patient's activities of

Table 3.2 Limitations in adaptive skill areas that originate prior to age 18 years associated with intellectual disability

Adaptive skill area	**Deficits**
Conceptual deficits	Receptive and expressive language, reading/writing/math, reasoning, and memory
Social deficits	Interpersonal communication skills, friendship, empathy, social judgment skills including gullibility and naiveté, and avoiding victimization
Practical deficits	Personal care activities: eating, dressing, bathing, meal preparation, telephone communication, and transportation Occupational skills: organizing school and work activities, money management, and job duties

daily life (ADLs) and instrumental activities of daily life (IADLs). As a basic assessment, determine if the patient is **i**ndependent, requires **a**ssistance, or is **d**ependent for a particular activity: ADLs (dressing, hygiene/self-care, and feeding) and IADLs (meal preparation, telephone communication, transportation, and financial management). There are several comprehensive assessments for individuals with developmental and intellectual disabilities including the Supports Intensity Scale, or "SIS," which evaluates practical support requirements of a person with an intellectual disability [24]. Assessing functional status requires a baseline appraisal with a goal of anticipating the short- and long-term needs of each patient.

Education

Many young adults with chronic health conditions may benefit from physician support of their educational development, including providing emotional support as well as essential documentation for schools. Eighteen percent of young adults with learning disabilities drop out of high school—three times the average dropout rate—and physicians may play a key role in encouraging students to continue formal education [25]. Only 13% of students with learning disabilities have attended a post-secondary school within 2 years of graduating high school (compared to 54% of the typical population) [26]. The Individuals with Disabilities Education Act (IDEA), which was brought into legislation in 1990, ensures that persons with disabilities are provided an individualized public school education. For those with ID, there are post-high school transition programs that provide an element of continued formation and education often including, but not limited to, ADLs and IADLs, social events/socialization, and vocational work. Educational transition planning can occur with the family and educators in the individualized education plan (IEP) generated for many students with learning disabilities. Many states have databases to register disabled people who are then selected for services as funding becomes available.

Living Arrangement and Family Support

Living situations vary and may range from independent living (with or without family or case manager involvement), living with nuclear or extended family, or living in a group home. The internist should have an understanding of the patient's living arrangement in order to gauge the level of support he or she is receiving or may require in future. An understanding of the patient's living situation can help guide a discussion regarding utilization of community resources and can help the provider evaluate the patient's goals and abilities.

Employment

Employment status will vary greatly in the AYA population and is dependent on their needs, skills, and opportunities available. All individuals with disabilities are eligible for vocational rehabilitation (VR) services through the local Department of Human Services. An individual who is eligible for Social Security Income benefits is also automatically presumed eligible for these services. VR services have benefit counselors who can guide young adults through the complicated requirements for eligibility for government benefits, such as Supplemental Security Income and Medicaid, while earning a paycheck.

Health Insurance and Benefits Relevant to the Transitioning Adult

Medicaid, Medicare, SSI, and SSDI

Supplemental Security Income (SSI) is a program that provides a monthly benefit and Medicaid coverage. Eligibility for Medicaid coverage begins after SSI benefit approval in 33 states. In 11 states, Medicaid eligibility begins after a separate application for Medicaid has been approved. Even if

individuals are approved in the pediatric setting, they must reapply at age 18. This means that the onus of initiating discussions regarding insurance transitions typically falls to pediatricians who care for patients until this time. Most adults age 18 and older with chronic health conditions meet the medical requirements and low-income criteria to receive SSI benefits.

Social Security Disability Income (SSDI) is to be distinguished from SSI. A work history for several years before being unable to work is required to be eligible for SSDI. Some young adults fall in this category of eligibility for both types of income.

Medical Decision-Making and Guardianship

When working with adult patients with chronic diseases of childhood, the question of guardianship and the legal-therapeutic relationship may go unaddressed until it threatens patient care. Additionally, many community resources such as schools and daycare programs that patients often utilize may cease to provide care as patients "age out" of their programs. Therefore, taking steps to ensure that patient-centered legal support is in place can streamline and ensure optimal care for each patient. At the initial visit, adult providers will need a quick assessment of the decision-making capacity of the young adult that has transitioned to their practice. Developmentally disabled adults are entitled to exercise their legal capacity just as individuals in the general population. Article 12 of the United Nations convention on the rights of persons with disabilities assures that they have equal rights and are provided the support they need to exercise their legal capacity [27]. If the individual is capable, a shared decision-making role may be established. Supported decision-making allows the adult-aged patient with disabilities to retain his or her decision-making capacity. Examples include decisions about managing money, healthcare, living situation and companions, and daily activities.

If an individual has need for supported decision-making, there is a range of supplemental aids that are alternatives to full guardianship, and these vary from state to state. These aids are the least intrusive measures to the patient's autonomy and should be considered. Options include a guardian of the estate, limited guardianship, joint bank accounts, representative payee, community advocate, and trustee (Table 3.3).

Full guardianship is required for adults with intellectual disabilities, and physicians make the assessment of decision-making capacity. Competence is a legal term and is determined by the courts. Guardian applicants are typically parents and family members who have determined that the patient does not have the capacity to make his or her own decisions. The physician role is to complete the healthcare provider certification supporting the patient's inability to make either medical or personal decisions. A primary care provider, subspecialist, or behavioral health specialist may complete this documentation. Guardian applicants typically have 90 days from the time the physician certification is completed to petition the courts for guardianship. Consultation with a lawyer by the guardian may be necessary to coordinate the guardianship process.

Table 3.3 Alternatives to full guardianship

Title	Responsibilities
Guardian of the estate	Responsible for the individual's finances
Limited guardianship	Limited to medical decision-making
Joint bank account	Guardian can monitor spending, requires both signatures
Representative payee	Person who manages funds received by government agencies, such as social security
Community advocate	Allows an agent to advocate on an individual's behalf with administrative and government agencies
Trustee	An individual who controls funds and other assets

Table 3.4 Advance directive/medical decision-making alternatives

Advance directive	Definition
Living will	Patient's wishes for end-of-life medical care when unable to communicate decisions
Durable powers of attorney for property and healthcare	Legal authority to make decisions on another's behalf when the patient is unable to do so
Advance directives in healthcare proxies	Designate a healthcare agent ahead of time; patient must be competent when appointing an individual

For all patients, regardless of decision-making status, it is important to have discussions about a living will, durable power of attorney for property and healthcare, and advanced directives and healthcare proxies (Table 3.4).

Local Resources for Intellectual and Developmental Disabilities (IDD)

Each state has an office for IDD. The state agency is an important resource for short-term or long-term services, particularly around residential and vocational/day programs. Individuals with chronic health conditions should register with the state-specific office. Each state also has an Aging and Disability Resource Center (ADRC) (https://www.adrc-tae.acl.gov) which provides a database of community resources broken down into local areas. Additionally, each state has at least one University Center for Excellence in Developmental Disabilities (UCEDDs) (https://www.aucd.org). Adult providers should be familiar with these agencies as they provide information on programs, advocacy, legal resources, and consumer guidance for the developmentally disabled population.

Unique Considerations in Teens and Young Adults with Chronic Health Conditions Transitioning to Adult Providers

When caring for young adults with chronic diseases of childhood, an internist will encounter two types of patients: specialist-dominated care and internist-dominated care.

Specialist-Dominated Care

Specialist-dominated care includes patients whose medical conditions are best managed with frequent visits to subspecialists, such as type 1 diabetes mellitus, cystic fibrosis, and congenital heart disease. In this type of care, most health-related decision-making is completed with the subspecialist, as these patients often have few, albeit complicated, health problems. Young adults transitioning to adult providers often need support finding an adult subspecialist with expertise in their chronic disease. This may take the form of a referral from their primary pediatric provider, primary pediatric subspecialist, or their new internist. Patients who receive specialist-dominated care utilize internists to ensure that all their primary care needs are met and that they are receiving correct age-appropriate screenings. Furthermore, internists shouldn't neglect appropriate AYA-related care, including HEADDSS interviews (**H**ome/family/community environment, **E**ducation plans, **E**mployment goals, **A**ctivities, **D**iet, **D**rugs, **S**ex education/contraception, **S**uicide/mental health) tobacco/alcohol/drug use screening, and HIV/STI testing and counseling, if appropriate.

Internist-Dominated Care

Medical conditions commonly managed by internist-dominated care include cerebral palsy, intellectual disability, autism spectrum disorders, and genetic disorders (e.g., Down

syndrome, William syndrome, fragile X). These patients tend to rely more heavily on internists because they have multiple healthcare needs which must be coordinated between several subspecialists. Physicians must be attentive to their population's primary care needs as well as help their patients navigate the complex network of social resources in the community. With internist-dominated care, the primary care physician is responsible for coordinating care between necessary specialists, ancillary care, and community resources. The onus of understanding the medical complexities of the patient's condition, as well as the appropriate primary/preventative care, falls on the internist. Routine screenings, STI/HIV testing, and young adult primary care should be offered alongside special medical care for the patient.

Condition-Specific Medical Knowledge

When caring for adolescents and young adults with chronic health conditions, adult providers have multiple resources to increase their condition-specific medical knowledge. As these are childhood-onset conditions, the American Academy of Pediatrics (AAP) publishes guidelines on the management of most chronic diseases. Additionally, the ACP and Got Transition have online resources which include disease-specific materials for common AYA with chronic medical conditions. Finally, there is emerging adult literature on the management of chronic childhood conditions including *Care of Adults with Chronic Childhood Conditions* by Pilapil et al. [28]. Readily available resources during an initial visit can facilitate transition and improve quality of care for AYASHCN. Table 3.5 outlines some sample diseases and their long-term management.

Table 3.5 Common comorbidities in the management of AYA with chronic diseases [29–31]

Common comorbidities with suggested long-term management strategies of young adults with chronic diseases of childhood		
Cerebral palsy	Contractures, scoliosis	Orthopedic evaluation
	Constipation	Aggressive bowel regimen
	Dysphagia/aspiration	Periodic speech evaluation
	Gastroesophageal reflux disease	Feeding by gastrostomy tube
	Decubitus ulcers	Frequent evaluation
Genetic syndromes (trisomy 21, Prader Willi, Williams)	Acquired valve dysfunction (MVP most common)	Baseline echo, then periodically
	Behavior disorder	Screen at each visit
	Celiac disease	Consider serology
	Hearing loss	Yearly hearing exam
	Iron-deficiency anemia	Assess yearly
	Sleep apnea	Screen as needed
	Thyroid dysfunction	Annual screening
	Visual loss (cataracts, keratoconus)	Eye exam every 3 years
	Obesity, hypertension	Annual screening
Epilepsy	Polypharmacy	Evaluation of meds and side effects
	Sports/activity evaluation	Must be seizure free to drive
	Driving evaluation	
Autism spectrum disorder	Higher rates of physical conditions: allergies, asthma, gastrointestinal problems, epilepsy	
	Higher rates of mental health conditions: ADHD, sleeping disorders, anxiety/depression	

Medication Reconciliation/Polypharmacy

With building independence, there is a shift in responsibility as young individuals with childhood chronic conditions are assuming more responsibility for their medications and healthcare. These individuals are at a higher risk for polypharmacy than their counterparts in the general population. A review of medications with the patient and caregiver if applicable allows providers to understand the patient's level of readiness to take an increasing role in his/her healthcare. It is important to review the adverse effects of long-term medications such as antiepileptics which increase the risk of osteoporosis [32] and phenothiazine, which can cause weight gain and QT prolongation that increases the risk for reentrant tachycardias [33].

Secondary Medical Conditions

Adult providers routinely customize care based on their patient's medical conditions. In the case of teens with chronic childhood conditions, customized care requires an awareness of associated or secondary conditions that may occur in this population. Secondary conditions refer to those conditions that a person with a preexisting disability experiences at a higher rate than the general population and are generally regarded as preventable [34]. For example, adults with juvenile idiopathic arthritis (JIA) are more at risk for pain, anxiety, and depression than their peers [35].

In general, there are multiple secondary and coexisting conditions seen at a higher frequency in teens with chronic conditions originating in childhood including behavioral health problems (see below), obesity, vision and hearing problems, hypothyroidism, congenital heart disease, chronic pain, epilepsy, and gastrointestinal problems including constipation and gastroesophageal reflux disease [36–38].

Behavioral Health

Children and young adults with chronic health conditions have a higher risk of behavioral conditions. Data links chronic disease with dysthymia [39], depression [39], and anxiety [40]. Primary care providers have an opportunity to address new behavioral issues or worsening of an existing behavior disorder at follow-up visits. Underlying medical causes of behavioral changes should be considered. Pain and distress are common causes of behavioral changes and can be assessed with the caregiver's help and pain assessment tools. There are multiple primary care toolkits to assess behavior changes provided by the American Academy of Pediatrics and Got Transition [18]. These assessments incorporate physical, environmental, and emotional factors. Table 3.6 outlines some commonly used screening tools for psychiatric conditions.

Anxiety and Depression

Youth with chronic disease have a higher incidence of anxiety than their peers in the general population [40]. Several risk factors have been identified including female gender, severity of chronic disease, time from diagnosis, and living in a single-parent household. Anxiety in children with chronic disease tends to present with more externalizing behaviors as well as

Table 3.6 Screening tools for common psychiatric comorbidities

Psychiatric condition	**Screening tool**
Depression	PHQ-9
Generalized anxiety disorder	GAD-7
Obsessive-compulsive disorder	Florida obsessive-compulsive inventory
Post-traumatic stress disorder	PC-PTSD
Behavioral disorders	SSBD, BASC-2

somatic complaints. Young adults may express anxiety by crying, tantrums, freezing, or clinging. Other qualifiers of anxiety (including separation anxiety) may be present in young adults who have learning or other developmental disabilities.

Depression is also extremely prevalent in persons with chronic disease [39]. Similar to anxiety, it may present differently than in older adults. For example, teens and young adults may present with irritability in lieu of depressed mood or anhedonia. A careful evaluation and mental status exam can be used to evaluate this population for depression.

Health Maintenance

Regarding preventive care of individuals transitioning to adulthood, the American Academy of Pediatrics (AAP), American College of Physicians (ACP), and American Academy of Family Physicians (AAFP) recommend applying the same guidelines for primary and preventive care for all adolescents and adults, including those with special healthcare needs. Examples of such guidelines include the American Medical Association's *Guidelines for Adolescent Preventive Services* (GAPS) and the US Public Health Service's *Guidelines to Clinical Preventive Services*.

Sexual Health

Sexual health is often overlooked in young adults with chronic diseases of childhood. With this group, it is often assumed that they are not sexually active. Sexuality and sexual relationships are not addressed appropriately in the healthcare setting [41, 42]. Although physically disabled adolescents may have delayed puberty and may be more socially isolated, they are as sexually experienced as their nondisabled counterparts [43]. The need for comprehensive sex education in this population is great, and discussion of sexuality, contraception, and abuse must be a standard part of anticipatory guidance for all teenagers with chronic conditions.

Sexual Abuse

Young men and women with invisible chronic diseases are more frequently victims of sexual abuse when compared to their typical controls [44]. In addition, the US Department of Justice reports that 68–83% of women with developmental disabilities will be sexually assaulted in their lifetimes and less than half of them will seek assistance from legal or treatment services [45]. There are many factors contributing to the increased risk of abuse including limited education and decision-making, dependence on others for care, exposure to a large number of caregivers and settings, inappropriate social skills, inability to report abuse, and lack of strategies to defend themselves [46]. As much as possible, the same discussions about sexual and reproductive health should occur with the patient and/or caretaker.

Contraception

There are a variety of reasons to provide contraception. As discussed above, there is a higher rate of sexual abuse. Contraception can also be used for therapeutic amenorrhea and to treat dysmenorrhea and menorrhagia. In severely disabled individuals, therapeutic amenorrhea is useful for those who are frightened or for whom hygiene is difficult. Both contraception and the possibility of sexually transmitted diseases should be addressed, and it ideally should occur directly with patients if they are autonomous.

Cervical Cancer Screening

The current American College of Gynecology guidelines recommends that women aged 21 and older have Pap tests every 3 years [47]. There are several studies to show that women with disabilities are less likely than those without a disability to report receiving a Pap smear in the past 3 years [48].

A practical approach may be to have an initial Pap smear and then modify frequency based on the individual's sexual activity and risk for abuse. Some women with disabilities such as cerebral palsy may require accommodations including extra support staff, positioning modifications, and a lengthier visit. However, these modifications should not preclude performing the pelvic exam. Every attempt should be made to provide the same health preventive guidelines for the individuals with chronic health conditions/developmental disabilities as provided for the general population.

Health Disparities

Adults with intellectual disabilities experience inequities in health status at a disproportionately higher rate than the general population [49]. The difference in health status is multifactorial. Health disparities can be due to the underlying condition, negative determinants of health such as poverty, and the differences in healthcare access or quality of services [50]. In general, individuals with chronic health conditions have fewer resources and are less equipped to navigate the healthcare system. Some of these patients may be underinsured and may need help accessing initiatives such as food stamps/supplemental nutrition support, utilities assistance, and affordable housing. Physicians can improve healthcare access for these patients by providing referrals to a social worker and information for local resources.

Ethical Considerations

Those who care for adults with childhood illnesses contemplate bioethical principles as they deal with guardianship, shared decision-making, healthcare disparities and school modifications, sexual health needs, and end-of-life discussions. Providers sometimes consider quality of life in determining both screening and medical treatment decisions. A 2010 study

showed that nondisabled people believe that the quality of life of people with disabilities is extremely low. However, when disabled people rate their own quality of life, it is only slightly lower than when nondisabled people self-report their own quality of life [51]. The literature shows that healthcare professionals' opinion of the quality of life of people with disabilities is lower than both the general public and the disabled individual's own opinion [52]. Thus healthcare providers must be aware of their potential bias when discussing treatment options for medical conditions and screening procedures.

Conclusion

Most adult providers have a limited number of teens with chronic health conditions transitioning to their practice; there are multiple components to the successful transition of youths with chronic illnesses from pediatric to adult providers. Pediatricians should encourage families to stay involved during the transition process while helping patients to become more autonomous and encouraging increasing self-care. There are a variety of uncommon and medically complex primary diagnoses, numerous secondary health conditions, and substantial coordination of care with subspecialists required. Physicians should plan increased time with these patients as well as additional time outside the office visit to coordinate services and provide care. Additional resources such as a social worker and dedicated nursing are often required. The challenges of caring for young adults with chronic disease of childhood come early, and anticipating these challenges becomes the responsibility of the primary care physician. The ultimate goal is to attain high-quality, longer lives free of preventable disease, disability, injury, and premature death; eliminate health disparities; and create social and physical environments that promote good health for all.

Clinical Pearls

- Request and review all documentation from the patient's pediatrician. Review past medical history, with attention to birth history and developmental history.
- Assess for polypharmacy, discuss long-term adverse reactions, and assess need for continued treatment.
- Assess patients' functional status, and define status based on the ability to perform activities of daily living (ADLs), e.g., feeding, dressing, toileting/self-hygiene, and IADLs, e.g., grocery shopping, meal preparation, telephone communication, financial management, and medical decision-making—described as **i**ndependent, requires **a**ssistance, or is **d**ependent for a particular activity.
- Review specific medical considerations; common comorbidities affecting patients with chronic diseases.
- Review condition-specific medical guidelines; AAP, Got Transition, and *Care of Adults with Chronic Childhood Conditions* by Pilapil et al.
- Psychiatric diseases are comorbid with chronic diseases of childhood; many screening tools are available to evaluate for common psychiatric conditions.
- In patients who do not have decision-making capacity, counsel family regarding legal guardianship or alternatives that allow for shared decision-making, advance directives, and end-of-life care.

Don't Miss This

- Anticipate lapses in insurance, and ensure that your patients will remain insured while under your care.
- Provide routine young adult/adolescent care when working with transition-age patients (e.g., HEADSS screening, alcohol and tobacco counseling, STI/HIV testing and counseling).
- Discuss sexual health early and often starting at the initial transition visit.
- Recognize biases in the quality of life considerations that may affect care.

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Chapter 4
Care of the Elderly Patient

Veronica M. LoFaso

Introduction

The population of the USA is rapidly aging. Currently 16% of the US population is over 65 years of age, and by 2040 approximately 21.6% will be over 65 years of age [1]. This demographic imperative necessitates a health care work force well trained in caring for older adults. The current number of geriatric specialists will not be adequate to care for the growing number of older adults [2]. Primary care practitioners will be doing most of this care and will need to be trained in the special syndromes that accompany aging: the geriatric syndromes.

The overarching goals of geriatric care include the following:

1. Enhancing function and promoting independence
2. Judicious use of diagnostic tests and procedures
3. Respect for patients' goals of care and health beliefs

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4. Simplifying medication regimens and deprescribing whenever appropriate
5. Providing team-based interventions that involve patient, family, and caregivers to achieve patient's health goals

Outpatient Assessment

The evaluation of the older adult includes the traditional components of a comprehensive history and physical exam but should be augmented with a more psychosocial, environmental, and functional focus. Obtaining a clear history can be challenging given the complexity of medical illnesses and the time constraints placed on most clinicians. Identified barriers to effective communication with older adults include the following:

- Sensory impairments
- Cognitive impairment
- Health literacy
- Presence of a third person in the interview (caregivers, home attendants, etc.)
- Tendency for some older adults to underreport symptoms
- Atypical presentation of disease

Tips for Effective Communication

- Evaluate the patient in a well-lit room facing the patient.
- Conduct interview in a quiet environment with the practitioner speaking clearly.
- Cognitively impaired patients will need caregivers present to assist with the history, but the patient should always be involved in the interaction.
- Interview patient alone to allow expression of personal concerns.
- Avoid speaking with the caregiver instead of addressing the patient directly.

- Listen actively to the patient's agenda and acknowledge his/her concerns.
- Avoid medical jargon.

Past Medical and Surgical History

A complete medical and surgical history should be conducted as done routinely on the adult patient.

Social History

- The social history is a critical component of a complete evaluation of the geriatric patient. Obtaining a robust social history allows for a deeper doctor-patient relationship and builds trust. It will also help avoid agist assumptions, aid in making the correct diagnosis, and obviate the need for unnecessary testing. The following should be included:
  - Education level
  - Family makeup and dynamics, social supports
  - Living situation, environmental hazards
  - Work history, economic status
  - Exercise, habits (smoking, alcohol)
  - Spirituality, cultural beliefs
  - Sexuality
  - Health care goals, health care proxy, living will, end-of-life wishes
  - Character strengths, resilience, coping skills

Medications

At each visit a careful review of medications should be performed reconciling new and old medications and removing any unnecessary medications. Dosing and timing of medications should be simplified, and attention should be paid to

cost and side effect profiles of all medications prescribed. Patients should be prompted to recall any and all recent visits to other providers that may have resulted in additional or duplicative medications. Assessment for use of any over-the-counter medications or supplements should be reviewed.

Review of System for Older Adults

- General: weight loss, sleep disturbance, fatigue
- HEENT: hearing loss, visual impairment, dysphagia, dental problems
- Cardiovascular: decreased exercise tolerance, chest pain, dyspnea on exertion, edema, palpitations, syncope, claudication
- Pulmonary: chronic cough, SOB, wheezing
- GI: difficulty chewing, constipation, diarrhea, rectal bleeding, melena, abdominal pain, easy satiety, dysphagia, GERD, hoarseness, fecal incontinence
- GU: urinary incontinence, hesitancy, frequency, hematuria, dysuria, UTIs, prolapsed bladder, sexual dysfunction
- Musculoskeletal: arthralgia, muscle aches, swelling, weakness, back pain, mobility impairments, falls in the last year
- GYN: vaginal bleeding, discharge, prolapsed uterus, dyspareunia
- CNS: headache, memory loss, weakness, dizziness, visual disturbances, tremor, neuropathy, gait instability
- Skin: rashes, skin breakdown, new growths/moles
- Psych: anxiety, depression, delusions, hallucinations, suicidal thoughts

Physical Examination: Evaluate for Pertinent Findings in the Geriatric Patient

- Vitals: BP (with orthostatic readings), pulse, temperature, BMI (weight change)
- HEENT: SNELLEN, whisper test, cataracts, cerumen, dentition, thyroid

- Chest: rales, rhonchi, wheezing, poor excursion
- Breasts: masses, skin changes, discharge, axillary adenopathy
- Cardiovascular: carotid bruits, murmurs, edema, pulses, irregular rhythm
- Abdomen: tenderness, scars, distention, organomegaly, costovertebral tenderness, bladder size
- GYN: discharge, uterine prolapse, bleeding, vaginal atrophy
- GU: prostate enlargement
- Rectal: rectal: tone, hemorrhoids, rectal prolapse, fecal impaction
- Skin: new moles, pigmentation, turgor, rashes, pressure ulcers
- Neurologic: tremor, gait impairment, weakness, reflexes, cranial nerves, tone, sensation, Romberg, cogwheel rigidity

Functional Assessment

Performing a functional assessment (Table 4.1) can greatly enhance the evaluation of the older adult in the following ways:

- Ensures patients will have treatments tailored to their individual level of capability

Table 4.1 Procedure for functional assessment screening in the elderly

Target	Assessment procedure	Abnormal result	Suggested intervention
Vision	Test each eye with jaeger card while patient wears corrective lenses (if applicable)	Inability to read greater than 20/40	Refer to an ophthalmologist

(continued)

Table 4.1 (continued)

Target	Assessment procedure	Abnormal result	Suggested intervention
Hearing	Whisper a short, easily answered question such as "what is your name?" in each ear while examiner's face is out of view	Inability to answer question	Examine auditory canals for cerumen, and clean if necessary. Repeat test; if still abnormal in either ear, refer for audiometry and possible prosthesis
Arm	Proximal: "touch the back of your head with both hands" Distal; "pick up the spoon"	Inability to do task	Examine the arm fully (muscle, joint, nerve), attending to pain, weakness, and limited range of motion Consider referral to physical therapy
Leg	Observe the patient after asking: "rise from your chair, walk 10 feet, return, sit down"	Inability to do task	Do full neurological and musculoskeletal evaluation, attending to strength, pain, range of motion, balance, and traditional assessment of gait. Consider referral for physical therapy

Table 4.1 (continued)

Target	Assessment procedure	Abnormal result	Suggested intervention
Urinary incontinence	Ask: "do you ever lose your urine and get wet?"	Yes	Ascertain frequency and amount. Search for remediable causes including local infections, polyuric states, and medications. Consider urologic referral
Nutrition	Weigh the patient. Measure height	Weight below acceptable range for height	Do appropriate medical evaluation
Mental status	Instruct: "I am going to name three objects (pencil, truck, book). I will ask you to repeat their names now and then again in a few minutes from now"	Inability to recall all three objects after 1 min	Administer Folstein MMSE. If score is <24, search for causes of cognitive impairment. Ascertain onset, duration, and fluctuation of overt symptoms. Review medications. Assess consciousness and affect. Do appropriate laboratory tests

(continued)

Table 4.1 (continued)

Target	Assessment procedure	Abnormal result	Suggested intervention
Depression	Ask: "do you often feel sad or depressed?"	Yes	Administer geriatrics depression scale. If positive (normal score, 0–10), check for antihypertensive, psychotropic, or other pertinent medications. Consider appropriate pharmaceutical or psychiatric treatment
ADL-IADL	Ask: "can you get out of bed yourself?" "Can you dress yourself?" "Can you make your own meals?" "Can you do your own shopping?"	No to any question	Corroborate responses with patients' appearance; question family members if accuracy uncertain. Determine reasons for inability (motivation compared with physical limitation). Institute appropriate medical, social, and environmental interventions

Table 4.1 (continued)

Target	Assessment procedure	Abnormal result	Suggested intervention
Home environment	Ask: "Do you have trouble with stairs inside or outside your home?" Ask about potential hazards inside the home with bathtubs, rugs, or lighting	Yes	Evaluate home safety and institute appropriate countermeasures
Social support	Ask: "Who would be able to help you in the case of illness or emergency?"		List identified persons in the medical record. Become familiar with available resources for the elderly in the community

Lachs et al. [3]

- Allows for monitoring response to interventions and medications
- Predicts mortality and morbidity [4, 5].
- Prognosticates likely outcomes from surgery or chemotherapy
- Identifies new diagnoses
- Determines proper level of assistance in the home and proper housing options

Health Promotion and Disease Prevention

Health promotion and disease prevention strategies should always consider the individual's health beliefs and goals and life expectancy. The risk and benefit of each intervention should be carefully weighed before subjecting patients to unnecessary or potentially harmful interventions.

Vaccines for Individuals over 65 Years of Age [6]

Influenza: High-dose IIV (Fluzone High-Dose) vaccine is recommended yearly given throughout the flu season [6].

Pneumococcal: Vaccination with PPSV23 is recommended for all individuals >65 years of age. Prevnar 13 is no longer routinely recommended unless the patient is immunocompromised, has asplenia, cerebrospinal leak, or cochlear implants or hx of invasive pneumococcal disease. The use of Prevnar 13 vaccine in those with chronic medical conditions (cardiac, pulmonary, diabetes, smokers, etc.) can be decided on an individual basis.

Tdap: One booster dose if never vaccinated. Tdap should be give regardless of when last Td or tetanus was received. Repeat Tdap every 10 years [7].

Herpes zoster: RZV (Shingrix) vaccine is recommended for most immunocompetent individuals >50 years of age. Two doses given at 0 and 2–6 months. Caution should be used in patents with history of Guillain-Barre, autoimmune disorders, and transplant recipients [8].

Primary and Secondary Disease Prevention

The US Preventive Services Task Force is an excellent reference for age-appropriate screening procedures. See www.uspreventiveservicestaskforce.org [9].

Calculating life expectancy can be a helpful guide when considering which interventions to institute for an older adult. See www.eprognosis.org [10].

Lifestyle and Behaviors

- Exercise: Physical activity in older adults should focus on moderate-intensity aerobic activity, muscle-strengthening activity, having an active lifestyle, and risk management. A goal of 150-min moderate aerobic exercise/week including 2 days per week of muscle-strengthening activity and balance exercises (e.g., Tai Chi) [11].
- Alcohol-NIH recommends no more than seven alcoholic beverages per week and no more than three alcoholic beverages on any given day for older adults.
- Smoking cessation should be encouraged, and use of nicotine replacement therapy as needed.
- Social supports: Data show that individuals with robust social networks who remain engaged in activities and have purpose have better health outcomes [12].

Geriatric Syndromes

Geriatric syndromes are clinical syndromes commonly encountered in older adults.

Urinary Incontinence (See Table 4.2)

Table 4.2 Types of urinary incontinence

Type	Gender	Amount	Risk factor	Complaint	Timing	Treatment
Urge	M = F	Large	Idiopathic; post-stroke; local bladder abnormalities Lesions in the inhibitory nerve pathways	Sudden need to void	Day and night (N > D)	Antimuscarinic Bladder regimen
Stress	F > M	Small	Multiple or large births; postmenopausal estrogen loss; pelvic floor weakening; obesity; sphincter failure (men)	Leakage with coughing or sneezing or exercise	Day	Kegel exercises Pessary
Mixed (stress + urge)	F > M	Variable	See above	Leakage with exercise, coughing-sense of urgency	Day and night	Antimuscarinic Kegel exercises

Functional	M = F	Variable	Functional impairment; mobility disorder	Can't make it to the bathroom	Day and night	Environmental modification; assistive devices
DHIC	M = F	Variable	Overactive detrusor	Incomplete emptying. Elevated post void residual	Day and night	Beta3-adrenergic agonist (Mirabegron)
Overflow	M > F	Dribbling	Outlet obstruction-prostate enlargement; cystocele	Dribbling; hesitancy; weak stream Elevated PVR	Day and night (D > N)	Alpha-blockers, type II 5-alpha-reductase inhibitors, TURP

DHIC detrusor hyperactivity with impaired contractility

Dementia (See Chapter on Cognitive Impairment)

Dementia is a progressive neurocognitive disorder manifested by decline in mental function that results in significant functional impairment usually affecting individuals after age 65. Approximately 5.1 million people over the age of 65 have Alzheimer's disease and dementia [13]. Caring for the needs of patients with dementia, which is fulfilled mostly by family and friends, often results in financial, psychological, and physical stress. It is crucial when evaluating a patient with dementia to consider the caregivers and support them throughout the course of this difficult disease. Social work consultation is often needed and appreciated by families. Referral to dementia support groups, elder lawyers, and geriatric care managers is a useful intervention for caregivers.

- www.alz.org/caregiversupport
- www.dementiasociety.org

Delirium

Although delirium is more often encountered in the inpatient setting during acute illness, it can still be encountered in the outpatient setting and must always be distinguished from dementia and depression. For the diagnosis of delirium, the CAM (Confusion Assessment Method) method can be utilized.

Confusion Assessment Method (CAM): Short version [14]

1. Acute onset and fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

Diagnosis of delirium must have #1 and #2 and either #3 or #4.

Delirium can manifest as either *quiet delirium* or *active delirium*. In the former patients may seem sedate, disengaged, sleepy, and withdrawn, and this presentation can be easily overlooked and ascribed to the patient being fatigued or depressed. In reality *quiet delirium* can be a life-threatening condition resulting from sepsis, stroke, hypercarbia, or dehydration among other considerations. *Active delirium*, which can manifest with agitation, hallucinations, and even violent behavior, is much less likely to be overlooked as the caregiver can easily see the patient is distressed and is therefore more likely to intervene.

Delirium Evaluation

- Assess vital signs: fever, tachycardia, orthostatic changes.
- Complete examination: especially neurological and cardiac exams, signs of urinary retention or fecal impaction.
- Check pulse oximetry and blood gas if indicated: hypoxia, hypercarbia.
- Check glucose and electrolyte measurements: hypoglycemia, hypernatremia, hyponatremia, hypercalcemia.
- EKG: MI, arrhythmia.
- Review of medications.
- Consider drug or alcohol ingestion or withdrawal.
- Ascertain any history of psychiatric illness.
- Imaging of the brain: CVA, tumor, hemorrhage.
- Environmental factors: lack of sleep, light deprivation, sensory impairments.
- Assess for untreated pain.

Management of delirium is targeted at treating the underlying condition.

Behavioral and environmental modifications can help reorient the delirious patient. Controlling pain, ensuring adequate sleep, treating dehydration, and improving oral intake can all help to reorient the patient. Establishing a sleep-wake cycle, having family and friends at bedside, and avoiding unnecessary interruptions by staff throughout the night can all be helpful interventions. Lastly, ensuring den-

tures, glasses, hearing aids, and home assistive devices are present can all give patients a sense of normalcy and increase their engagement with their environment.

The use of antipsychotic medications is reserved for situations where the patient is a danger to self or others. Olanzapine (2.5–5 mg), risperidone (0.5 mg), haloperidol (0.5 mg), and quetiapine (12.5–25 mg) are available as needed. EKGs should be done periodically to monitor QTc while on antipsychotic medications.

The prognosis for delirium is generally recovery within a few days of treating the underlying condition; however, cases of protracted delirium do occur and can last weeks to months. Pharmacologic interventions should be evaluated daily and discontinued as soon as possible.

Depression

Although depression is commonly seen in older adults, it should not be considered a normal part of aging. Untreated depression can lead to adverse health outcomes and significant impairment in the quality of life. Late-onset depression is more likely to be of vascular etiology rather than genetic origin and may even be a harbinger of early dementia [15].

Medication Management

Dosing should start low and be titrated up slowly. Older patients will usually need the full dose to achieve therapeutic effects. The full therapeutic effect on mood may not be seen for 4–6 weeks after initiating treatment. Therapy should continue for approximately 6–12 months after the therapeutic effects have been reached for the first-time episode of depression.

1. **SSRIs** are the first-line treatment

   Sertraline or citalopram. **Side effects**: GI upset, hyponatremia, upper GI bleeding, decrease bone mineral density.

2. **SSRI nonresponders**
   - Mirtazapine: enhances appetite, anxiolytic, helps with insomnia
   - Bupropion: more stimulating
   - Venlafaxine: more energizing; may be useful for somatic pain. Follow BP
   - Duloxetine: may be useful to improve chronic pain
3. **Additional options**
   - SSRI plus Bupropion
   - Augmentation of SSRI with quetiapine or aripiprazole
   - Electroconvulsive therapy can be very effective in medication non-responders and in those with vegetative symptoms

Falls and Immobility

Falls and their sequelae are the leading cause of death from injury in the >65-year-old population. The prevalence of falls in those >65 is about 30% in community-dwelling older adults and about 50% for those over 80 years of age [8]. The incidence of a second fall occurring within the same year as an initial fall is 60%. The causes of falls are usually multifactorial. One should evaluate for ay contribution from environmental or medical factors (Table 4.3). Older adults presenting with a fall should be carefully queried about the circumstances and timing of the fall as falls are often a presenting sign of medical illness [16].

A careful history is key to determining the cause of a fall. Some useful questions include the following [16]:

1. **Can you describe the circumstances surrounding your fall?** What happened? Was the cause mechanical?
2. **Did you lose consciousness?** If so, this is syncope and needs a syncope evaluation.
3. **Did you feel lightheaded or as if you were going to faint?** Vasovagal episode.

Table 4.3 Assessing fall risk

Risk factors for falls	Medical conditions associated with falls
Previous falls	Infection (UTI; pneumonia)
Gait instability	Electrolyte imbalance
Dizziness	Orthostatic hypotension
Orthostatic hypotension	Arrhythmia
Polypharmacy[a]	Musculoskeletal disorders (OA)
ADL impairment	Medication side effects
Muscle weakness	Sensory impairments
Age >80	Neurological disorders (Parkinson's; MS)
Vision impairment (multifocal lenses); cataracts; macular degeneration	Alcohol use
Environment: stairs; clutter; rugs	

[a]Medications include sedative hypnotics, anxiolytics, muscle relaxants, diuretics, opiates, neuroleptics, and anticholinergic medications

4. **Did you feel the room spinning around?** Suggests vertigo.
5. **Did you lose urine or stool?** Seizure may be the cause of the fall.
6. **Did you have palpitations?** Suggests possible arrhythmia.
7. **Any new medications?** Suggests adverse drug effect.

Examination of the Older Adult After a Fall [16]

- **Gait, balance, and mobility assessment**: Detailed assessment of gait, balance, mobility, and lower extremity joint function (crepitus, effusions, ROM).
- **Neurological function including cognitive evaluation**: Evaluate lower extremity peripheral nerves, proprioception, reflexes, tests of cortical, extrapyramidal, and cerebellar function; check for cogwheeling and rigidity.
- **Muscle strength**: Test lower extremities for strength and range of motion.
- **Cardiovascular status**: Complete a thorough cardiovascular and pulmonary assessment. Check the following: heart

rate and rhythm, orthostatic vital signs, and presence or absence of peripheral edema.
- **Visual acuity assessment**.
- **Foot and footwear examination**.
- **Laboratory**: Electrolyte abnormalities, anemia, and signs of infection (UTI).
- **Radiology**: As indicated by examination.

Get Up and Go Test [17]

Instructions: Ask the patient to perform the following series of maneuvers:

- Sit comfortably in a straight-backed chair.
- Rise from the chair.
- Stand still momentarily.
- Walk approximately 3 m.
- Turn around.
- Walk back to the chair.
- Turn around.
- Sit down in the chair.

Scoring: Observe the patient's movements for any deviation from a confident, normal performance. Use the following scale: 1 = normal, 2 = very slightly abnormal, 3 = mildly abnormal, 4 = moderately abnormal, and 5 = severely abnormal. A score of 3 or more increased the risk of falling. <10 s = normal; >20 s = further evaluation and intervention needed.

Preventing Future Falls

- Reduce all meds to minimum doses needed particularly psychoactive meds.
- Home safety and environment evaluation by visiting nursing service.
- Physical therapy evaluation for strengthening and balance exercises.

- Review proper footwear and ensure proper assistive devices.
- Treat visual impairment.
- Ensure adequate hydration and nutrition.

Polypharmacy

Older adults with multiple complex medical problems are at risk for accumulating excessive medications prescribed by multiple practitioners—commonly referred to as "polypharmacy." At every office visit, medication reconciliation is imperative. It may be advisable to have the patient bring in all of their home medications including over-the-counter medications at regular intervals for review. Removing potentially harmful, duplicative, or unnecessary medications in the elderly should be the focus of the medication reconciliation process. Ask about the use of supplements. Careful attention should be paid to renal and hepatic function before dosing any medication. The American Geriatrics Society has compiled a list of potentially inappropriate medications for older adults—the *AGS Beers Criteria* [18].

Sensory Loss

Vision

Impairment in vision can have a significant impact on the quality of life in the older adult. Impairments in vision can lead to social isolation, falls, car accidents, and depression. The four most common eye disorders in the elderly are as follows:

1. *Cataracts*: (lens opacification) blurring of vision; sensitivity to glare
   Treatment: surgery, lens implants

2. *Age-related macular degeneration (AMD):* atrophy of cells in the central macula region of retina leading to loss of central vision
   - Wet (neovascularization) *treatment*: intravitreal injections of VEGF inhibitors; vitamin and mineral supplementation
   - Dry (focal deposition of drusen) *treatment:* observation; vitamin and mineral supplementation
3. *Glaucoma:* (increased intraocular pressure causing optic nerve damage) loss of peripheral vision. *treatment:*
   - Open-angle: pharmacologic therapy.
   - Narrow-angle requires immediate evaluation by ophthalmology-laser treatments or surgery.
4. *Diabetic retinopathy: (*hemorrhages and microaneurysms) *treatment*: laser therapy/photocoagulation

Hearing Loss

Presbycusis is the most common type of hearing loss in older adults characterized by a sensorineural, symmetrical loss generally affecting the high registers. Patients may initially report tinnitus in the early stages of loss. Initial presentation should include an examination to exclude cerumen impaction. Unilateral hearing loss requires a more in-depth evaluation by an otolaryngologist with concerns for tumors or other structural etiologies.

Tips for communicating with the hearing impaired patient are as follows

1. Let the patient relate the best way to communicate.
2. Avoid background noise.
3. Speak slowly but avoid shouting and use a deep voice.
4. Sit facing the patient ideally 2–3 feet away and on the side of the better ear.
5. Use written words or gestures if needed.
6. Ask the patient to repeat back what he/she heard.

Malnutrition and Unexplained Weight Loss

Unexplained weight loss is a common and concerning presenting problem in the geriatric population. Weight should be measured at each office visit and is considered a vital sign in the care of older adults (Table 4.4).

Osteoporosis

Osteoporosis is considered one of the geriatric syndromes. Fractures resulting from osteoporosis can lead to significant morbidity and mortality. Mortality is 25% at 1 year, and only 75% of patients will recover to their prior level of function after a hip fracture [14]. Identification and treatment of

Table 4.4 Evaluation of malnutrition

Causes	Signs of malnutrition	Interventions
Advanced dementia Malignancy Depression Chronic infection Inflammation Hyperthyroidism Poor smell/taste Poor dentition Dysphagia Advanced chronic illness Social isolation/ access to food	BMI <22 kg/m^2 Loss >5% BW in 1 month Loss >10% BW in 6 months Low albumin or pre-albumin Low cholesterol (<160 mg/dL) Sarcopenia Vitamin deficiency (B12, vitamin D) Reduced hand grip	Treat underlying medical or psychiatric disease Medication review Encourage social eating and assess food preferences Evaluate food consistency/ dental evaluation Nutritional supplements Allow adequate time for meals Swallowing evaluation Consider appetite enhancers: • Mirtazapine • Cyproheptadine • Megestrol (cautious use risk of DVT and fluid retention)

osteoporosis is a fundamental part of maintaining function and preventing morbidity and mortality in older adults.

Consider FRAX score (Fracture Risk Assessment Tool—WHO) for assessing the 10-year probability of fracture when considering treatment. See www.shef.ac.uk/frax [15].

Sleep Disorders

Sleep disorders are highly prevalent in the older population. Older adults have reduced total sleep time, increased time to fall asleep, more daytime napping, and reduced REM sleep. Approach to insomnia should include evaluation of pain, nocturia, symptoms of sleep apnea or restless leg syndrome, and consumption of caffeine or alcohol. Management options include sleep hygiene measures, cognitive behavioral therapy, relaxation techniques, and pharmacological interventions:

- Melatonin: Start at 2–4 mg.
- Sedative hypnotics (zolpidem, 5 mg; eszopiclone, 1 mg): Use sparingly and with caution for falls, excess daytime fatigue, and confusion.
- Short-acting benzodiazepines (lorazepam, 0.5 mg): Use sparingly.
- Trazodone: Start at 25–50 mg.

Advanced Care Planning

Working with patients and families to establish end-of-life preferences can prevent unwanted medical interventions and reduce suffering. The following topics should be addressed with patient and family:

- Living will: document establishing medical choices at the end of life.
- Health care proxy: identifying a person of trust for health care decisions.

- MOLST (Medical Orders for Life-Sustaining Treatment) form.
- Housing/living options as care needs advance: social work referral.
- Financial planning: wills, trusts. Consider referral to elder lawyer.

Elder Abuse and Neglect

It is estimated that one in ten older adults is a victim of elder mistreatment. Types of elder mistreatment include psychological, physical, financial, and sexual abuse as well as neglect. Unfortunately only 1 in 24 cases of abuse are identified [15]. Victims of abuse were found to have a threefold increase in all-cause mortality compared to non-abused elders. The majority of abusers are either family members or other individuals close to the victim, and medical practitioners are often the only contact with the outside world. Screening for elder abuse should be done with the patient alone to ensure confidentiality and to avoid any influence from the suspected abuser.

Evaluation for elder abuse should include the following:

1. Identifying risk factors for victimization (dementia, physical impairment, social isolation)
2. Identifying characteristics of abusers (substance abuse, mental illness, dependence on victim, history of animal abuse)
3. Evaluating the family dynamic (cycle of violence, caregiver stress)
4. Identifying motive for abuse or neglect (financial gain, housing)
5. Assessing for mental illness or substance abuse within the home

There are several elder abuse screening tools that can be helpful:

(a) EASI-Elder Abuse Suspicion Index [19].
(b) Hwalek-Sengstock Elder Abuse Screening Test
(c) VASS-Vulnerability to Abuse Screening Scale

If the clinician has suspicion for abuse or neglect, a complete social work evaluation should be initiated and consideration given to involving police, Adult Protective Services, and local district attorney's offices. Safety planning and involvement with local social service agencies is crucial to provide a needed network of support for the patient.

Home Care

As our population ages, patients are living longer with more chronic illnesses. At the same time, hospitals are incentivized to discharge patients sooner to curb the ever-rising health care costs. This backdrop makes home visits an appealing health care delivery model for many homebound and chronically ill patients.

The AMA describes the role of the physician in home care as not only providing in-home medical care but being an active member of the team that establishes a treatment plan with short- and long-term goals of care for the patient. The physician is involved in documentation of care, certification of needed services, and providing continuity between care settings. In addition, close communication with and support of caregivers as well as other team members is an important role for the physician (Table 4.5) [21].

TABLE 4.5 Sample house call checklist (based on the INHOMESSS pneumonic) [20]

Impairments/immobility

Evidence of cognitive impairment?
☐Yes ☐ No

Demonstrated advanced activities of daily living (check all that apply):
☐ Employment/volunteering
☐ Reading
☐ Music
☐ Hobbies
☐ Socialization
☐ Other

Demonstrated activities of daily living (check problem areas):
☐ Ambulating
☐ Toileting
☐ Transferring
☐ Bathing
☐ Feeding
☐ Continence (bowel/bladder/both)
☐ Dressing

Demonstrated instrumental activities of daily living (check problem areas):
☐ Taking medications
☐ Finances
☐ Telephone
☐ Transportation
☐ Meal preparation
☐ Shopping
☐ Housework
☐ Driving

Demonstrated balance and gait (check problem areas):
☐ Balance
Static (Romberg test, standing reach test)
Dynamic (walking, tandem walk)
☐ Gait
Left: arm swing, stance, leg swing, step
Right: arm swing, stance, leg swing, step

Sensory impairments (check problem areas):
☐ Hearing
☐ Vision
☐ Smell
☐ Taste
☐ Tactile

Falls?☐ Yes☐ No

Nutritional status and eating habits

Eating habits: _____

Variety and quality of foods

Pantry: _____

Refrigerator: _____

Freezer: _____

Nutritional status

Obesity: _____

Malnutrition: _____

Other: _____

Fluid intake: _____

Alcohol presence/use: _____

Swallowing difficulty: _____

Oral health: _____

Home environment

Neighborhood: _____

Exterior of home: _____

Interior of home (check all that apply)
☐ Crowding
☐ Good housekeeping
☐ Hominess
☐ Privacy
☐ Pets
☐ Books
☐ Television
☐ Memorabilia
☐ Internet
☐ Information and communication technology

Other people

Caregiver? ☐ Yes ☐ No

If yes, who? _____

Tasks:

Hours of caregiving per day: _____

Stress? _____

Coping? _____

Abuse? _____

Need for respite? _____

Physically or emotionally capable? _____

Social supports? ☐ Yes ☐ No

Advanced directives? ☐ Yes ☐ No

Power of attorney? ☐ Yes ☐ No

If so, who? _____

Financial resources: _____

Patient attitude: _____

Medications

Prescription drugs: _____

Nonprescription drugs: _____

Dietary supplements: _____

Medications organized: _____

Medication compliance: _____

Medication discrepancy: _____

Multiple prescribers: _____

Allergies to medications: _____

Written instructions: _____

Examination

Weight: _____ Weight loss? _____

Height: _____ Blood pressure: _____

Glucose: _____ Urinalysis: _____

Other: _____

Mini-Mental State Examination: _____

Depression screening: _____

General physical condition: _____

Focused examination: _____

Safety (check all that apply)
☐ Access to emergency services
☐ Alternative power source if needed
☐ Adaptations to home needed
☐ Telephone availability
☐ Bathroom
☐ Kitchen
☐ Carpets
☐ Lighting
☐ Electrical cords
☐ Stairs
☐ Tables, chairs, and other furniture
☐ Hot water heater
☐ Fire and smoke detectors
☐ Fire extinguishers
☐ Emergency plans
☐ Evacuation route
☐ Gas or electric range
☐ Heating/air-conditioning
☐ Water source

Spiritual health (or cultural and ethnic influences): _____

Services (e.g., fire, police, emergency medical services, home health, social services, Meals on Wheels, hospice, transportation, legal, equipment, health benefit advisor):
_____
_____

Clinical Pearls

- Be aware of black box warning for cardiac events with antipsychotics.
- When using antipsychotics, follow EKG for prolongation of QTc.
- Avoid antipsychotic use in patients with Parkinson's or Lewy body dementia-can consider quetiapine use in dire situations.

- Benzodiazepines generally worsen delirium unless being used for delirium related to ETOH withdrawal.
- In the treatment of depression as with all meds in the geriatric population, start with low doses and titrate to therapeutic dose. Maintain therapeutic dose for 6–12 months.
- In the treatment of depression, monitor for side effects such as hyponatremia in the first weeks of treatment and periodically thereafter.
- In the treatment of depression, avoid highly anticholinergic medications which may cause hypotension, sedation, and falls, e.g., tricyclic antidepressants (imipramine, doxepin, amoxapine, trimipramine).
- Be familiar with the Beers criteria to avoid medications that should not be used in older adults. See: Beers Criteria: onlinelibrary.wiley.com/doi/10.1111/jgs.1370
- In treating insomnia, avoid diphenhydramine. Evaluate carefully for fall risk before prescribing any sedating medications.

Don't Miss This!

- Minimize use of medication whenever possible. Review the patients' medication list at every visit, and remove unnecessary and duplicative medications. Review the Beers criteria to avoid medications that can be harmful to older adults.
- Assessing and improving function and social supports is a major focus of geriatric care.
- Care of the older adult is best delivered by a multidisciplinary team including social work, physical and occupational therapy, and mental health and nutrition services.
- Advanced directives and goals of care should be clarified initially and updated periodically with any change in health status.
- Dementia care requires education and support of the patient and caregiver. Recognizing and alleviating caregiver stress should be part of good dementia care.

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Chapter 5
Care at the End of Life: Palliative and Hospice Care—Symptom Management

Tabitha N. Goring and Ingrid L. Nelson

History

The modern palliative care movement began in Great Britain in 1967 when Dame Cecily Saunders founded St. Christopher's Hospice in London. She had been inspired by one of her patients, a Polish refugee named David Tasma. Tasma had survived the Holocaust—the only member of his family who did—and emigrated to London where he worked in a restaurant. In 1947, he was diagnosed with cancer. Dame Saunders cared for him at the end of his life, and they formed a very close attachment. In their conversations she realized that, along with his physical suffering, he was struggling to under-

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stand the meaning of the life he had lived—why he had survived while so many others had died—as he approached his own death. When he died, Tasma left a bequest to Saunders, predicting: I'll be a window in your home.

At St. Christopher's, Dame Cecily and her colleagues formulated the first principle of palliative care: that the experience of serious illness is physical, emotional, and spiritual and that attention to all three domains is necessary to successfully treat any one. The logical corollary that a team of physicians, nurses, social workers, pastors, and psychologists need to be involved followed. The model that Dame Cecily developed was an early instance of patient-centered care, and this is how she described its focus and power: "You matter because you are you, and you matter to the last moment of your life. We will do all we can, not only to help you die peacefully, but also to live until you die."

Today, palliative care is recognized on every continent, and in almost every country, as a medical subspecialty. In the United States, at last count, more than 70% of hospitals with more than 50 beds have a palliative care service.

Palliative Care/Hospice Care

The introduction of focused palliative care, in addition to standard medical care, is appropriate for patients with serious illnesses who have significant symptom burdens no matter the stage of their disease (Fig. 5.1). In the United States, patients with heart failure, COPD, liver disease, dementia, and serious cancers are the most common candidates; patients with ALS, PD, renal disease, and advanced AIDS will also benefit. The goal is to ameliorate symptoms such as pain, SOB, and anxiety and also provide patients and their families with social and spiritual support. Inpatient palliative care is typically delivered by a team that includes physicians, nurses, social workers, pastors, and psychologists; outpatient palliative care teams should follow the same

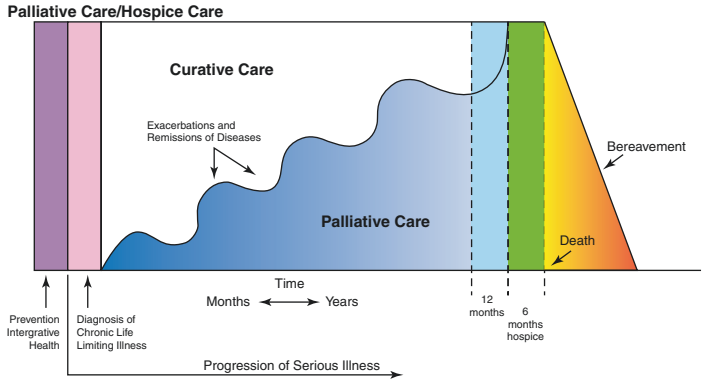

FIGURE 5.1 The increasing importance of palliative care and hospice as disease progresses. From: Roth, Alan R.; Canedo, Angelo R. Introduction to Hospice and Palliative Care. Primary Care: Clinics in Office Practice.2019-09-01, Volume 46, Issue 3, Pages 287–302, Copyright © 2019 Elsevier Inc.

model, as much as possible. The ultimate goal is to improve quality of life by the following:

- Providing pain and symptom control.
- Helping family members care for the patient.
- Informing patients about treatment options and their risks and benefits.
- Helping patients prepare for the future.
- Giving patients and their families a sense of control.

Along with improving quality of life, the early introduction of palliative care has been shown to have another, unexpected benefit: an increase in life span. In a study published in the New England Journal of Medicine in 2010 [1], 151 patients with newly diagnosed metastatic NSCLC were randomized into two groups: one received standard oncologic care and one received standard oncologic care along with early integrated palliative care. Those in the second group had less pain and depression, received less chemotherapy, and lived longer—results that have given impetus to the establish-

ment of palliative care services in hospitals across the country. Palliative care also saves money: a JAMA meta-analysis published in 2018 concluded that hospitalized patients who received palliative care in addition to routine treatment used fewer medical resources and were less costly to treat [2]. Thus, the benefit of palliative care is both humanistic and practical—a fact not lost upon the medical administrators who support it, and a reason for the introduction of dedicated palliative care services in more outpatient settings.

Hospice care is for patients in the last 6 months of their lives. It has been a benefit under Medicare since 1986. As with palliative care, the focus of treatment is on symptom relief, quality of life, and family support, with care delivered by a multidisciplinary team. However, aggressive therapies such as hemodialysis and chemotherapy with curative intent are not part of hospice care. Hospice care can be delivered at home by a home hospice organization; this has the benefit of reducing emergency room visits and hospitalizations and improving the chances of patients dying at home, if this is their wish. It can also be given in a dedicated inpatient hospice setting or as an addition to regular care in a nursing home. Generally, patients with symptoms that need aggressive care or those who have little support at home will do best in these settings.

Role of the Primary Care Physician in Palliative Care/Hospice

Primary care physicians are in a perfect position to identify patients who will benefit from palliative care. Obvious candidates include patients with the following:

- High symptom burden
- Declining functional status
- New diagnosis of serious cancer

It is also helpful to consider the trajectory of diseases commonly seen in the outpatient setting (Fig. 5.2)

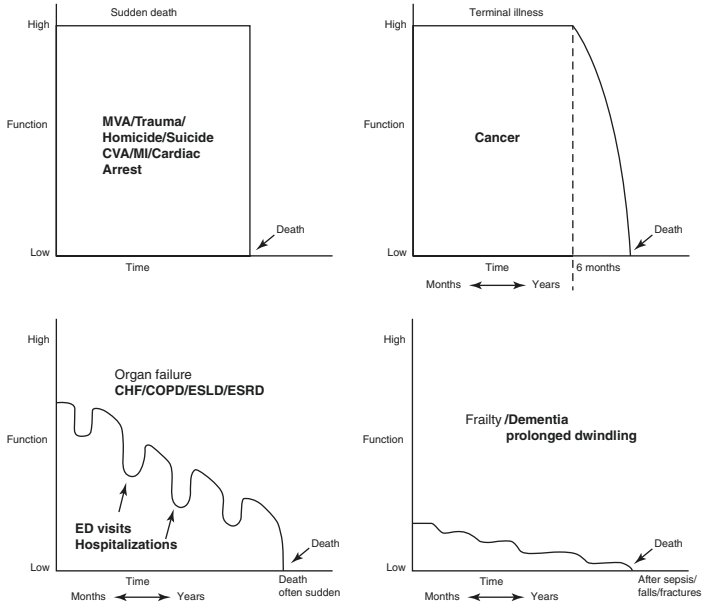

FIGURE 5.2 From: Roth, Alan R.; Canedo, Angelo R. Introduction to Hospice and Palliative Care. Primary Care: Clinics in Office Practice.2019–09-01, Volume 46, Issue 3, Pages 287–302, Copyright © 2019 Elsevier Inc.

This schematic provides rough prognostic information that can help time the introduction of palliative care in appropriate patients. Decline is rapid in patients with a serious cancer when effective treatment is no longer available. Patients with serious chronic diseases experience a slow decline punctuated by exacerbations, from which they only partially recover. Patients with dementia decline inexorably.

Prognostication needs to be more precise for hospice care because of the requirement that prognosis be 6 months or less. Serious cancers have the best validated prognostic models; prognostication for chronic diseases and dementia generally rely on a complex of symptomatology. Remember that these models are suggestions and not hard and fast rules, and it is common for hospice services to be renewed after

6 months. The CMS (Center for Medicare and Medicaid Services) has developed disease-specific criteria for hospice eligibility; below are criteria for diseases most commonly followed in a primary care setting. Information about other diseases (ALS, HIV, etc.) is available on their website [3].

CMS Hospice Eligibility

Dementia

- Unable to dress independently
- Unable to bathe independently
- Urinary and fecal incontinence
- Can speak only six or fewer words

Heart Disease

- Already on optimal treatment
- NYHA Class IV with symptoms at rest
- Supporting criteria: treatment-resistant symptomatic supraventricular or ventricular arrhythmias, history of cardiac arrest or resuscitation, history of unexplained syncope, brain embolism of cardiac origin, or concomitant HIV disease

Liver Disease

- INR >1.5 AND albumin <2.5
- One of the following: ascites, SBP, hepatorenal syndrome, hepatic encephalopathy, recurrent variceal bleeding
- Supporting criteria: malnutrition, alcoholism, HCC, Hep B, Hep C

Pulmonary Disease

- Severe disease documented by dyspnea at rest, poorly or unresponsive to bronchodilators, and progression of disease documented by frequent physician visits or hospitalizations
- Hypoxemia on room air or hypercapnia

- Right heart failure secondary to cor pulmonale
- Unintentional weight loss of >10% in the past 6 months
- Resting tachycardia

Renal Failure
- If acute: no dialysis, serum creatinine >8, comorbid conditions
- If chronic: no dialysis, GFR < 15, serum creatinine >8, and accompanying conditions such as uremia, oliguria, hyperkalemia unresponsive to treatment, uremic pericarditis, hepatorenal syndrome, and intractable fluid overload

If your patient does not clearly fit into any of these categories, ask yourself the palliative care gut question: Would I be surprised if this patient died within the next year? If the answer is no, evaluate for palliative care or hospice.

When to Refer

In complicated cases, palliative care should be delivered by a trained specialist. CAPC (Center to Advance Palliative Care) is a nonprofit organization that provides information about and educational resources for palliative care. Their website is an excellent source of information; this is their list of suggested triggers for referral to a palliative care specialist [4]:

- Multiple recent prior hospitalizations with same symptoms/problems.
- Declining ability to complete activities of daily living.
- Persistent weight loss.
- Difficult to control physical or emotional symptoms related to serious medical illness such as pain, depression, and constipation.

- Patient, family, or physician uncertainty re: prognosis or goals of care.
- Patient or family requests for futile care.
- DNR order conflicts.
- Use of artificial nutrition in seriously ill patients.
- Limited social support and a serious illness (e.g., homeless, chronic mental illness).
- Patient or family psychological or spiritual distress.

Starting the Conversation/Important Documents

Patients with whom you want to discuss advanced care planning need to want to discuss it too—the first step in starting the conversation is to assess your patient's willingness to have it. Visits arranged for the purpose of advanced care planning are covered by Medicare. Your goal in these conversations is to guide your patient in deciding what their goals of care are. For example, do they want to avoid going to the hospital, even if this means forgoing aggressive treatment that might be life prolonging? How much discomfort are they willing to tolerate? How involved do they want their families to be? Are there things they want to accomplish or events (graduations, weddings) they want to attend before they die? If they are from another country, do they want to spend the last part of their life there?

Each conversation will be different because, at heart, you are asking about your patient's most deeply held beliefs about the meaning of life and death, their role in their community, and the role of spirituality in their lives. When your patient is from another country, cultural differences will exist—talk of death, for example, may be unacceptable; when they are African American, they may have a lack of trust in the medical system that will influence their decisions about code status [5]. Cultural competency, the umbrella term for

these different ways of looking at care, is a huge subject and well beyond the scope of this chapter. However, if you try to understand your patient's perspective on their illness, and explore what is important to them now and what their hopes are for the future, you can work together to formulate goals of care.

Here are some initial considerations:

- Avoid medical terminology.
- Listen more than talk. Allow periods of silence.
- Respond to cues.
- Understand that patients almost always know how sick they are and that talking about it may be a relief.
- Make medical recommendations—remember, it's the family/patient's job to define their goals and your job to describe how their goals can be achieved.
- Make sure your patient knows that you will continue to care for them, no matter their decisions.

A useful structure for these conversations is the SPIKES protocol, which was developed by oncologist Robert Buckman in the late 1990s [6]. While its original intent was to help oncologists deliver bad news to their patients, it is equally applicable to conversations introducing palliative or hospice care. SPIKES is an acronym:

S for setting: It should be quiet, calm, and comfortable. Important family members, friends, and possibly clergy should be invited.

P for perception: What does your patient think about their health?

I for invitation: Ask your patient how much they want to know about their disease and its probable course.

K for knowledge: Give you patient warning that you are going to bring up some tough issues.

E for empathy: Respond to your patient's reaction.

S for strategy: End every conversation with a plan for the future, even if it's a plan for another conversation.

There are a number of legal and medical documents used in advanced care planning. The two most important are as follows:

- Health care proxy (HCP)—a form signed by the patient that names an alternate decision-maker if they are rendered incapable.
- MOLST (Medical Orders for Life-Sustaining Treatment) Form—a more specific set of medical orders, signed by a physician, detailing code status and level of medical interventions.

Both of these documents can help your patient to think more specifically about their goals. For example, the MOLST form addresses artificially administered nutrition, use of antibiotics, and future hospitalizations. And assigning an HCP will lead your patient to discuss what kind of care they want in the future with their HCP.

It's important not to focus too much on DNR/DNI (do not resuscitate/do not intubate) orders. Some patients might have firm opinions from the outset; some may not. DNR and DNI are a small part of advanced care planning.

Patients should keep copies of both these documents with them, especially when transitioning between different sites of care.

Management of Common Symptoms in Palliative Care

Almost all symptoms can be controlled in any setting with medications, with or without minimally invasive options. You will be using medications you are familiar with, but sometimes in different ways and at different doses. While it is important to arrive at a diagnosis, the main thrust of treatment is comfort: diagnostic tests should be used judiciously, and medications should be titrated to achieve comfort.

Shortness of Breath

Determine whether or not the patient requires an inpatient evaluation. Assess resting respiratory rate, pulse oximetry, and auscultate lungs for adventitious sounds. Shortness of breath (SOB) in a patient receiving palliative care should be evaluated as in any patient with SOB.

Once you've identified the underlying cause, discuss treatment options with your patient or their surrogate. Many episodes of SOB can be relieved with measures such as low-dose opioids, supplemental oxygen, antibiotics, diuretics, steroids, and treatment of anxiety. All these interventions can be administered at home, with hospice support. If more aggressive measures are required—i.e., fluid drainage—determine if these are in alignment with your patient's goals of care.

If intubation is on the table, tell your patient how likely it is that they will be successfully extubated. Assure them that you can keep them comfortable without intubation if that is their choice. Document your conversation and make sure their surrogate is aware.

In the actively dying patient, focus on comfort. Consider a cooling fan for air hunger. Oxygen via nasal cannula is the standard of care, but face masks can also be used. High-flow nasal cannula (HFNC) oxygen often cannot be administered at home, and the patient would have to be admitted to a facility—hospital or inpatient hospice for O_2 via this modality—if that is in keeping with the patient's goals. Opiates to treat tachypnea should be given as an infusion or in standing doses; there is no dose ceiling and the goal is to achieve a respiratory rate of 12 or less. Opioids can be delivered orally, sublingually, subcutaneously, transdermally, intrathecally, or via an intravenous drip (Fig. 5.3).

Constipation

Constipation is a very uncomfortable symptom and should be managed aggressively. Opioid use, dehydration from poor

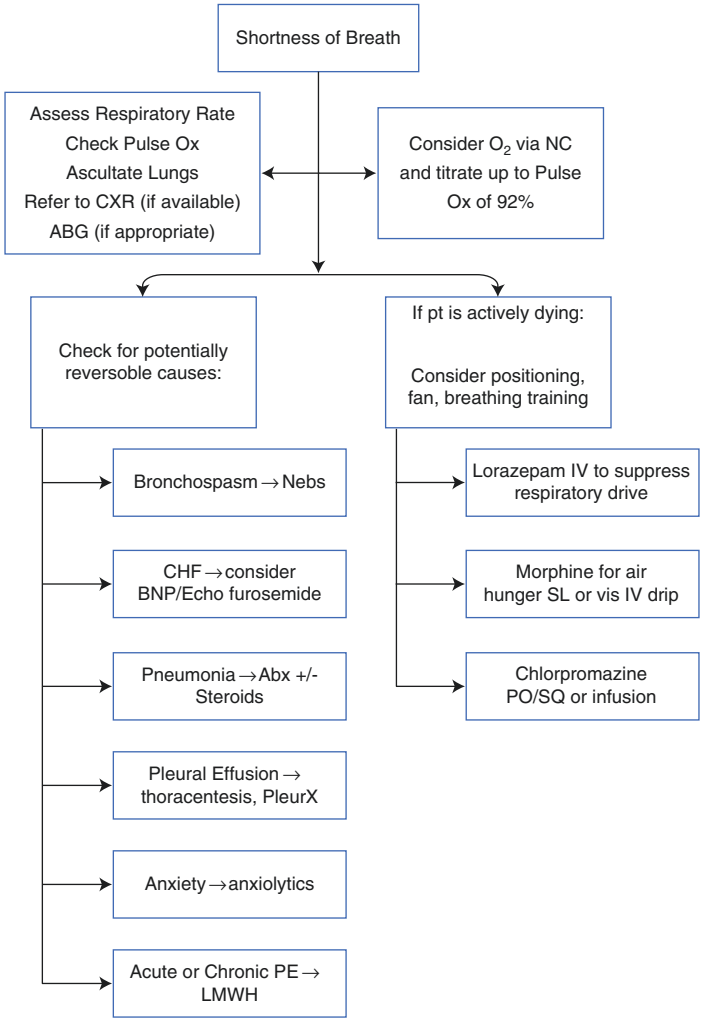

FIGURE 5.3 Algorithm for shortness of breath at the end of life

intake, vomiting, and limited mobility are the main factors that place this population at high risk for constipation.

Ask about stool frequency, opioid use, and other medications. On physical exam, assess hydration status, and look for

signs of obstruction or fecal impaction. Determine if there is an underlying, reversible medical cause that could be treated and if treatment of such a condition is congruent with the palliative goal. Non-pharmacologic lifestyle modifications should be tried before medications—discontinue, substitute, or adjust doses of constipating medications; increase fluid intake; increase fiber intake; and encourage mobility anorectal testing, colonic transit testing, defecography, and surgery which are invasive and unlikely to be beneficial in the palliative care population. Biofeedback or pelvic floor training should be considered.

Treatment includes stool softeners, laxatives (bulk, osmotic, stimulant), rectal suppositories, and enemas in escalating doses and combinations. There are currently no evidence-based guidelines on the order in which to give laxatives, but the American Gastroenterological Association provides guidelines for initial management of constipation [7]. Know the difference between stimulant (bisacodyl, senna) and osmotic (polyethylene glycol, lactulose, sorbitol, milk of magnesia, magnesium citrate) laxatives as well as the form and volume in which they are provided (pills vs. liquid). Some patients may have difficulty swallowing pills or be intolerant to sweet or large volume of liquids. Stimulant laxatives may cause excessive cramping. Prescribe the form most comfortable for the patient at the lowest dose to encourage a bowel movement (Fig. 5.4).

Nausea/Vomiting

Nausea is an uncomfortable feeling which often precedes vomiting. Both are protective mechanisms by which the body expels toxins, unsavory food, etc., but they can also be triggered by emotional causes and medications. The symptoms can originate in the CNS or the GI tract, and several mechanisms are usually involved. In the palliative care population, nausea and vomiting are most frequently caused by chemotherapy, opioid use (where symptoms usually resolve over time), obstruction/constipation, increased intracranial

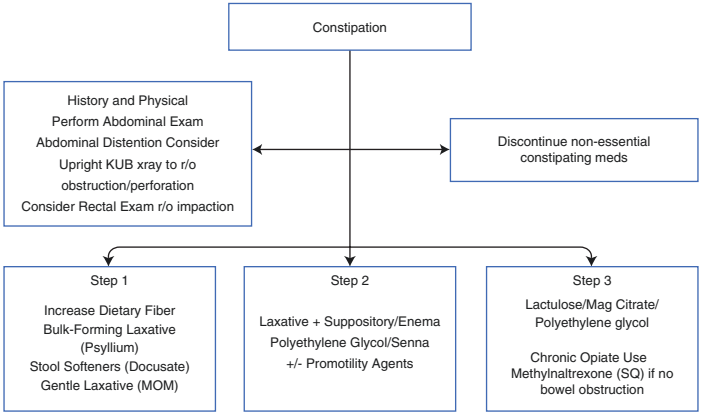

FIGURE 5.4 Management of constipation in palliative care

pressure caused by CNS lesions, metabolic disturbances (renal failure, hypercalcemia), and/or anxiety.

Determining the underlying etiology of the nausea/vomiting will help you choose the appropriate medication/intervention that will help. Commonly used treatments in palliative care are as follows:

- For drug effect: haloperidol, ondansetron (esp chemo related)
- For increased intracranial pressure: dexamethasone
- In ESRD: haloperidol, dose reduced
- For anticipatory nausea: benzodiazepines
- For ileus, gastroparesis: metoclopramide
- For obstruction: octreotide, dexamethasone
- No obvious cause: metoclopramide, dexamethasone

A multimodal approach is usually indicated. Choose agents with different mechanisms of action at the lowest effective dose (Fig. 5.5).

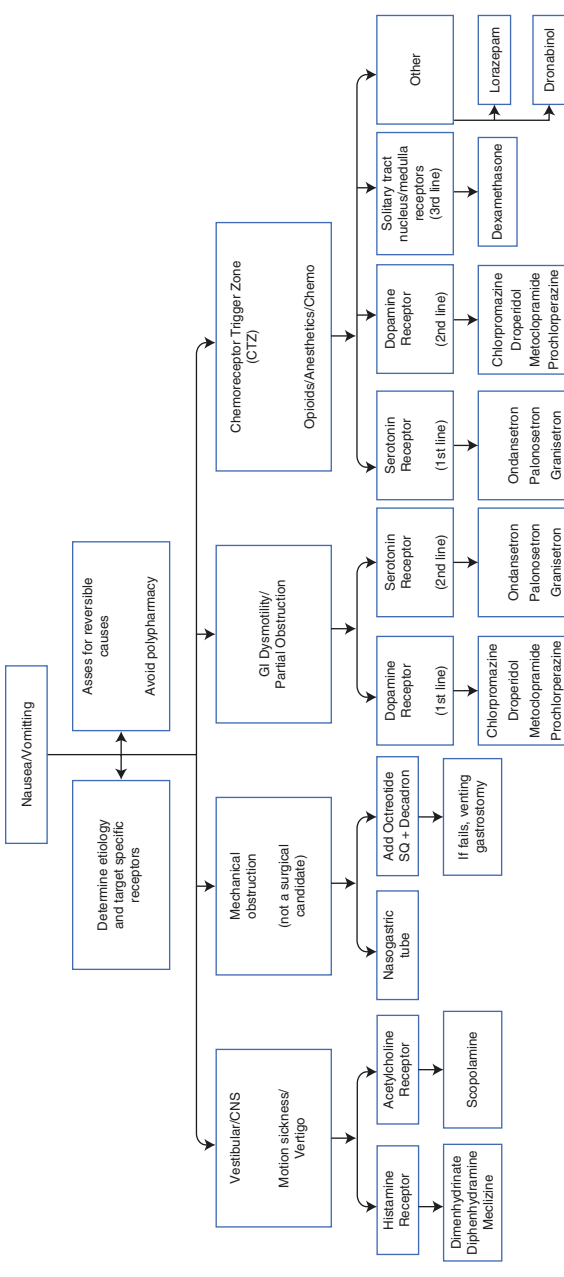

FIGURE 5.5 Assessment and management of nausea and vomiting in palliative care (Modified from *Flake, Z. Am Fam Physician.* 2004 Mar 1;69(5):1169–1174)

Pain

One of the first rules of palliative care developed by Dame Cecily Saunders is that continuous pain requires continuous treatment. Most palliative care patients have continuous pain, and so it is important to develop a treatment regimen that can be delivered around the clock. While opioids are a mainstay, adjuvant medications can provide a synergistic effect that may lessen the dose of opioids required.

Pain is divided into three broad categories. Visceral pain is usually abdominal, poorly localized, and deep and squeezing in nature. Somatic pain is usually incisional or musculoskeletal, well localized, and sharp in nature. Neuropathic pain results from nerve injury caused by chemotherapy, tumor compression, or radiation therapy and is burning or stinging in nature. These categories are important because they will determine which medications will be of most benefit. However, in practice, most pain is mixed in origin.

Adjuvant medications include acetaminophen and NSAIDS; unless there are contraindications, they should be part of all pain regimens. For visceral pain, anti-inflammatories like dexamethasone or prednisone are very effective. Somatic pain responds well to NSAIDS. Neuropathic pain responds best to tricyclic antidepressants and SNRIs and anti-epileptic drugs such as gabapentin and topiramate.

When beginning treatment with opioids, start low and go slow. Use oral formulations. Start with as needed (PRN) dosing of short-acting forms, and, when an effective dose has been established, change to long-acting formulations. Always continue PRN dosing of short-acting medications to treat breakthrough pain. And, always give medications for constipation—this is a side effect of all opioids and requires a stimulant. When dosing, remember that there is no ceiling dose for opioids—medications should be titrated until relief is achieved.

Anesthesia-based interventions (nerve blocks, intrathecal pumps, spinal stimulators) may be useful in certain regional pain syndromes. These interventions may be appropriate for patients with intractable side effects secondary to opioid use and/or patients on excessive doses of opioids by allowing the

patient to reduce or eliminate opioid use. Radiation therapy is also a useful pain treatment modality, especially in cases of cancer-related bone pain.

The World Health Organization (WHO) has developed a three-step ladder for cancer pain relief [8]; an algorithmic version is presented in Fig. 5.6.

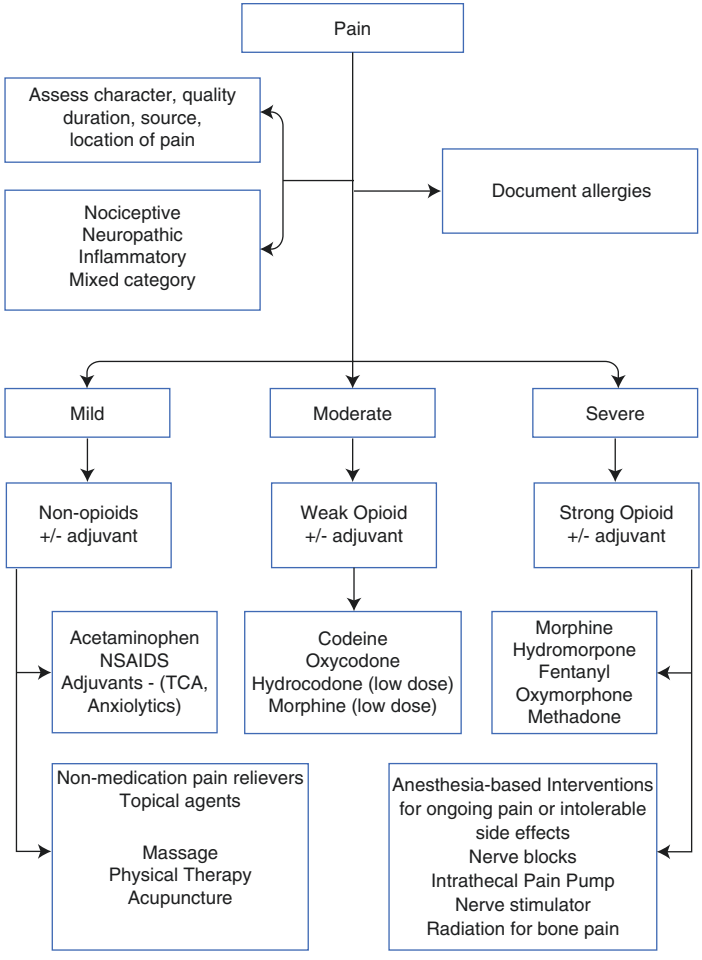

Figure 5.6 Management of pain in palliative care (Modified from WHO Stepladder)

Pain at the end of life also has an existential component—profound questions about the meaning of one's life and of things done and not done. Conversation with loved ones and spiritual advisors may help patients explore these questions. And, although controversial, evidence suggests that existential pain can be managed with acetaminophen [7].

Conclusion

Caring for patients at the end of their lives is an important part of primary care medicine. Decades of medical literature have shown that, at the end of life, most people hope for dignity, comfort, the company of loved ones, and peace—none of which can be found in an intensive care unit. By using the tools of palliative and hospice medicine in your practice, you can provide these things. While the task may seem daunting, the benefits to your patients are immeasurable.

Clinical Pearls

- Palliative care is specialized care for individuals with serious, often life-limiting illness.
- Patients with a predicted life expectancy of <6 months qualify for hospice care.
- Primary care physicians should feel comfortable discussing goals of care with patients.
- The two most important advanced care documents are the health care proxy and the MOLST form.
- Palliative care can be delivered concomitantly with disease-directed therapies.
- Goals of care discussions should happen early and be reassessed as things change.

Don't Miss This!

- Do not forget to evaluate for reversible causes of shortness of breath.
- Shortness of breath can be managed with oxygen and opioids at the end of life.

- Obstruction should be ruled out in a patient with nausea/vomiting.
- When treating pain, begin with non-opioid analgesics, if appropriate.
- Always prescribe a bowel regimen along with opioids.
- When giving multiple medications to control nausea/vomiting, choose those with different mechanisms of action.

Resources

CAPC website: a very valuable source of information, educational materials, and resources.

Oxford Textbook of Palliative Medicine. Oxford University Press. This is also available in a shortened, pocket sized version. A good source of information for assessment and treatment of symptoms.

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Chapter 6
Substance Use Disorder

Kimberly Cartmill

Introduction

Untreated alcohol and opioid use disorders lead to increased morbidity, mortality, and hospital spending [1]. Treatment for substance use disorder decreases mortality and prevents relapse [2–4]. Despite the availability of effective, evidence-based treatment, it is estimated that only 25% of patients with opioid use disorder and under 10% of patients with alcohol use disorder receive treatment annually [5]. Primary care providers have a unique opportunity to identity and engage patients with risky substance use and substance use disorders (SUD).

This chapter will focus on unhealthy use of alcohol and opioids. The same guidelines for screening and counselling apply to other substances, such as cannabis and cocaine. Alcohol and opioid use disorders are highlighted due to their prevalence and significant impact on individual health and

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society. In addition, opioid, alcohol, and tobacco are the only substance use disorders with FDA-approved medications which should be prescribed in the primary care clinic.

Definitions

Substance use exists in a spectrum and changes throughout a person's lifetime. While the majority of people in the United States consume substances like alcohol without risk of harm, it is estimated that 24% of primary care patients have risky substance use, and about 3% have a substance use disorder [6].

Unhealthy or *risky substance* use is defined as use that has the potential to cause harm. For prescription drugs, such as opioids or benzodiazepines, this would be any use of the medication in a way other than instructed [7, 8]. This includes taking a prescription opioid at a higher dosage or frequency than prescribed or for another indication. For illicit drugs, such as cocaine or heroin, any use is considered risky [7, 8].

This contrasts with alcohol, in which there is a definition of risky use [9, 10]:

- For women: drinking eight or more drinks in 1 week OR four or more drinks in one sitting.
- For men: drinking 15 or more drinks in 1 week OR five or more drinks in one sitting.

Substance use disorder (*SUD*) is a chronic relapsing brain disease that causes clinically significant impairment or distress. This diagnosis defined by the DSMV as having at least 2 of 11 criteria [11]:

- Using larger amounts/longer than intended.
- Repeated attempts to quit/control use.
- Craving.
- Much time spent using.
- Activities given up in order to use.
- Neglected major role in order to use.
- Physical/psychological problems associated with use.

- Hazardous use.
- Social/interpersonal problems related to use.
- Withdrawal*.
- Tolerance*.

Please note that withdrawal and tolerance WITHOUT other criteria does not qualify. These two criteria alone are physiological results of continued use known as dependence.

Decision-Making

Identification

The US Preventive Services Task Force recommends screening patients over the age of 18 for unhealthy alcohol and drug use [12, 13]. There needs to be a follow-up process for engagement or referral to treatment for positive screens. While the guidelines do not specify the recommended frequency, screening high-risk individuals (younger than 25 years; having a psychiatric disorder, nicotine or alcohol dependence; having experienced physical or sexual abuse in childhood; having a personal or family history of drug or alcohol addiction; having chronic pain; and having easy access to prescription drugs) on an annual basis seems reasonable.

There are validated screening tools available to identify and risk-stratify patients with unhealthy substance use. It is recommended that the patient independently and confidentially complete the screening. This starts with a one-question screen for alcohol and drug use [7, 14–16]:

- Alcohol screen [7, 14, 16].
  - Men: How many times in the past year have you had **five** or more drinks in a day?
  - Women: How many times in the past year have you had **four** or more drinks in a day?

A positive screen is 1 or above. This should be followed up with the AUDIT [17]. Please note that it is important to define a “standard” alcoholic drink when screening patients.

This is defined as 12 fluid ounces of beer (one standard can), 5 fluid ounces of table wine (one glass), and 1.5 fluid ounces of spirits (one shot glass).

- Drug screen [7, 15, 16]: How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?

A positive screen is 1 or above. This should be followed up with the DAST-10 [18, 19].

The DAST-10 and AUDIT scores risk stratify the patient into no or low risk, at risk, moderate/high risk and severe risk. This helps to identify the best treatment strategy for the patient (Fig. 6.1).

Key History

Patients with risky substance use and substance use disorder require special consideration. These patients have likely suffered due to stigma, a history of trauma, and co-occurring psychiatric conditions [20]. It is important to approach each interaction with respect and compassion. It should be emphasized that all physician-patient discussions are confidential while acknowledging that clinicians are mandatory reporters. If there is a concern that a patient's substance use is putting a dependent at risk, the appropriate authorities need to be notified.

The initial history taking in a patient with risky substance use is similar to any other visit. Although the clinician may be aware of the patient's substance use before the encounter, it is important to approach the patient with the same agenda-setting opening recommended for all patients. Beginning with open-ended questions such as "How can I help you today?" or "What would you like to discuss during this visit?" may prompt the patient to bring up substance use. However, many patients may not spontaneously disclose they would like to discuss this.

The clinician should bring up the patient's substance use if the patient fails to do so. This may be broached during the

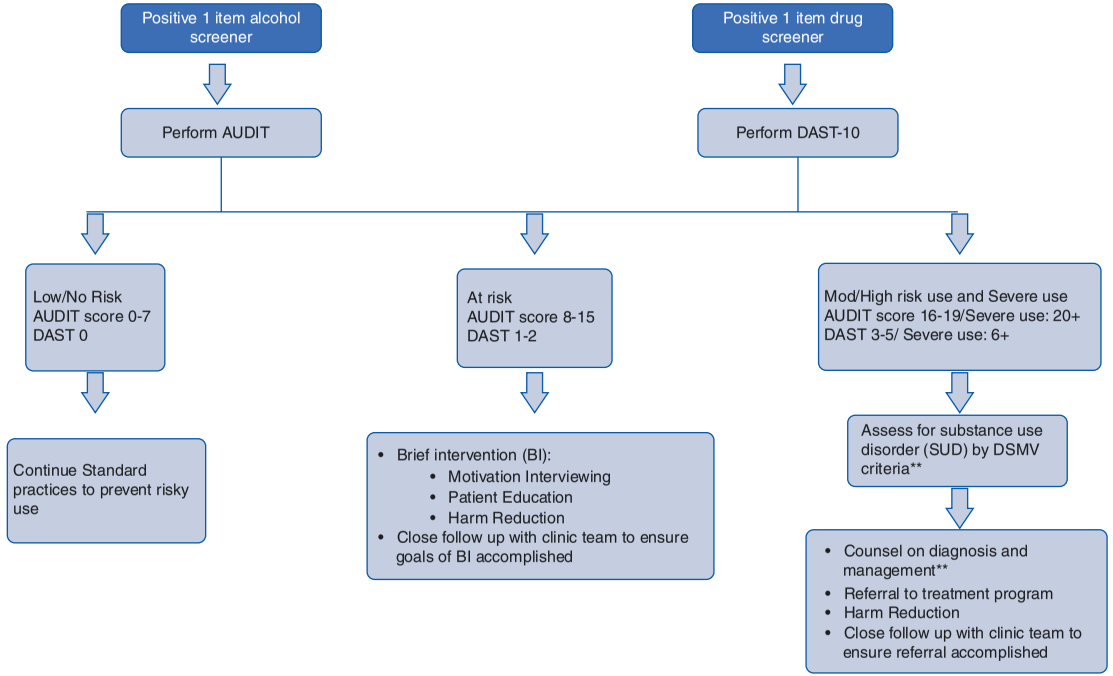

FIGURE 6.1 Proposed screening for unhealthy substance use in primary care [7, 16–19]

routine social history elicited at each new patient visit. While assessing the patient's tobacco, drug, and alcohol use, it is important to avoid leading questions. For instance, simply stating "How often do you drink alcohol?" and "How often do you use drugs or medication not prescribed to you?" are good opening questions. If a patient states he or she never drinks, an inquiry as to why is recommended as the majority of American adults have consumed alcohol at least once [21].

Prior to further discussion into a patient's substance use, it is recommended to ask permission. For instance, "Would it be OK to discuss this further?" or "I would like to learn more about your drinking, would that be OK?" If the patient agrees, the clinician can then continue with nonjudgmental questions to better understand the patient's own perspectives about current substance use and its consequences. A sample discussion would include the following:

Current use: Identify the type, quantity, route, and last use for each substance.

- Assess if there is sharing of materials used for intranasal or intravenous drug use. While risk of hepatitis and HIV transmission through sharing needles is common knowledge, the risk of sharing other supplies can be overlooked. For instance, hepatitis C can be acquired by sharing supplies such as water when injecting drugs [22]. Hepatitis C can even be found on straws used for intranasal drug consumption [23].

Consequences: Ask if their substance use has led to problems with the law, finances, employment, relationships, or health.

- Legal: incarceration, parole, and citations (such as driving under the influence).
- Employment or financial: job loss, bankruptcy, and housing insecurity.
- Relationship: neglect or abuse of dependents, loss of relationships, or parental rights.
- Health problems: liver, lung, heart, brain, or kidney disease; trauma; impacts on chronic disease management (diabetes, hypertension, heart failure); erectile disfunction;

and infections like HIV, STIs, cellulitis, abscesses, endocarditis.

  - Prior overdoses, as well as substance-related emergency room and hospital visits, should be documented.

Patient's impression of substance use:

- Has the patient thought about and/or tried to cut down prior?
  - If so, why? What happened?
- Does the patient think substance use is causing or contributing to any problems?
  - If no, do their friends or loved ones think so? If so, why?

If the patient expresses a desire to seek help for substance use during the visit, a more detailed substance use history can be pursued. The clinician can guide the patient to recount the substance use history from the first use until the present. This history may guide the management plan.

Workup

A detailed history guides the appropriate workup. The goal of laboratory or imaging studies is to determine if the patient has health problems related to substance use, ensure safety, and prevent substance-related diseases.

For patients with alcohol or opioid use disorders, initial laboratory analysis should include the following [20]:

- Complete blood count (CBC) to identify anemia and thrombocytopenia.
- Liver and kidney tests (CMP).
- Infectious disease workup: HIV antibody, hepatitis serologies (hepatitis A, B, and C); syphilis and tuberculosis testing can also be considered.
  - If patients lack immunity, provide vaccinations for hepatitis A and B.

  - If HIV negative and at high risk for acquisition, discussion of HIV pre-exposure prophylaxis is recommended.

- Urine tests: Toxicology is recommended for all. This can identify substances that patients may not be aware they are consuming.
- Pregnancy tests for women of child-bearing age.
- For patients with opioid use disorder, an EKG can be considered prior to starting methadone or suboxone to assess the patient's QT interval.

Management

Harm Reduction Any patient with risky substance use should have harm reduction counselling. Harm reduction is the concept of making risky behaviors less dangerous. Some examples include the following recommendations:

- Do not drive or operate machinery under the influence.
- Do not use alone.
- Do not mix substances.
- Do not share drug paraphernalia.

Any treatment plan should emphasize patient-centeredness and harm-reduction. Lecturing the patient or presenting abstinence as the only viable option could be harmful. While abstinence may be the goal for some patients, others may wish to cut down on their use to improve their financial, interpersonal, or health issues.

Risky or Unhealthy Alcohol Use

Low Risk These patients have an AUDIT score of 8–15. There is good evidence that providing patients with risky alcohol use with brief interventions can decrease their number

of binge-drinking episodes, emergency room visits, motor vehicle accidents, and arrests [24–27]. Brief interventions may consist of the following [7, 26–28]:

- Motivational interviewing.
- Targeted patient education.
- Providing concrete services (such as linking to assistance with housing, food, employment and education).
- Linking to care or therapy (including psychiatric care, group support, and psychotherapy).

Moderate to Severe Risk Patients with AUDIT scores of 16 or higher should be assessed for alcohol use disorder. They often need to be referred to behavioral therapy or a treatment program [7, 16].

Alcohol Use Disorder Management All substance use disorders are stratified by severity based on the DSMV criteria [11]:

- 2–3: mild
- 4–5: moderate
- 6+: severe.

The goal of alcohol use disorder treatment is to decrease relapses and mortality related to alcohol use. Patients with moderate to severe alcohol disorder who are interested in reducing alcohol intake should be offered medication-assisted treatment (MAT) [16]. This consists of medication with behavioral therapy. Behavioral therapy may consist of the following [28]:

- Individualized therapy, including cognitive behavioral therapy (CBT) or motivational therapy (MET).
- Twelve-step facilitation (such as group therapy, alcoholic anonyms, or smart recovery).

The primary care provider may refer these patients to psychotherapy with an experienced social worker, psychologist, psychiatrist, or addiction specialist. In addition to supplying the referral, the clinician has the important role of ensuring the patient was able to follow through with the recommendation and of troubleshooting potential barriers.

Behavioral treatment should be combined with medication to decrease relapse rates [27]. There are three FDA-approved medications for alcohol use disorder [29]: naltrexone, acamprosate, and disulfiram.

Disulfiram is rarely used due to poor compliance, adverse reactions, and drug interactions. It requires the patient be highly motivated and has better success with supervised administration. The patient must have no alcohol use 12 hours prior and 14 days after taking the tablet. The medication causes build-up of aldehyde leading to tachycardia, flushing, headache, nausea, and vomiting. There are several concerns with disulfiram, including increased risks of seizures, cardiac events, and liver toxicity [29].

Naltrexone and acamprosate are two medications that should be prescribed by primary care providers for the treatment of alcohol use disorder [26, 27, 29]. These medications should not be started if the patient is unstable or in acute alcohol withdrawal. Such patients should first complete detoxication, which should be in an inpatient setting or supervised by an experienced clinician. Outpatient detoxification in the primary care clinic is not recommended for any patient with a history of complicated alcohol withdrawal, including delirium tremens and seizures.

A patient should be started on naltrexone or acamprosate once treatment for acute alcohol withdrawal is completed. Some patients may not want to go through detoxification, opting to cut down on their alcohol use instead. If the patient is stable, the clinician could initiate naltrexone or acamprosate to help the patient reduce his or her intake.

The following is a brief description of each medication [29]:

Naltrexone: This is preferred over acamprosate due to less frequent dosing.

Mechanism: opioid receptor antagonist
Administration: either a daily oral tablet or monthly intramuscular injection

- Oral: may take with or without food. Administration after food recommended to reduce gastrointestinal side effects. To minimize side effects, can be started at 25 mg (cut 50 mg tablet in ½) for 1 week and then increase to the recommended dose of 50 mg daily.
- Intramuscular injection: 380 mg in gluteal muscle every 28 days.

Contraindications:

- Acute hepatitis or liver failure.
  - Liver enzymes (AST or ALT) over three times the upper limit of normal.
  - Decompensated cirrhosis.
  - Please note, It CAN be given with stable Child's Class A cirrhosis.
- Opioid use.
  - Naltrexone is an opioid blocker, so it can cause acute opioid withdrawal.

Common side effects: nausea, diarrhea; for injection: can cause injection site reactions
Acamprosate:
Mechanism: modulates glutamate receptors
Administration:

- Oral: may take with or without food. Recommended with food to increase compliance. Can start with 333 mg (one tablet) three times daily and titrate up to goal 666 mg (two tablets) three times daily.

Concerns:

- Renally dosed. A dose reduction is needed if creatitine clearance is 30–50.
- Contraindicated with creatitine clearance under 30.

Common side effects: nausea, abdominal discomfort, and dizziness

These two medications can be given together. Liver and renal function should be monitored at least every 6–12 months.

Risky Opioid Use or OUD

Harm Reduction In addition to the harm reduction counselling referenced above, there are specific strategies related to risky opioid use. Each patient should receive a naloxone kit. If none is available, assist the patient in obtaining one. Naloxone has been shown to reduce overdose death [30]. In addition, the clinician can inform patients of circumstances that put them at higher risk of overdose, such as using opioids after a period of abstinence [31].

Medication-Assisted Treatment Similar to AUD, patients with opioid use disorder (OUD) should be offered medication-assisted treatment (MAT). The behavioral interventions are similar to those used for alcohol use disorder. However, the emphasis on treatment with medication is even greater for OUD as robust evidence demonstrates significant decreases in morbidity and mortality [2].

There are three FDA-approved treatments for opioid use disorder maintenance: methadone, buprenorphine, and naltrexone. Only methadone and buprenorphine can be used to treat acute opioid withdrawal. After the patient is stabilized, these medications should be continued at a maintenance dose for at least 6–12 months. Failure to continue methadone or buprenorphine results in high relapse rates, poor retention in care, and increased use of illicit drugs [32, 33].

As discussed in the section on alcohol use disorder, primary care doctors can prescribe naltrexone. However, many patients with opioid use disorder have difficulty starting naltrexone because they must stop using opioids for 10–14 days prior to initiation [34]. Thus, methadone and buprenorphine are the most commonly used medications for OUD.

There are restrictions on prescribing buprenorphine and methadone for OUD. Methadone must be provided in a certified program; this cannot be prescribed by the primary care provider. Buprenorphine is often prescribed by a certified primary care provider, psychiatrist, or addiction medicine specialist. Primary care providers gain certification by completing a brief training and obtaining a X-waiver from the DEA. Even if the clinician is not prescribing the medications, it is important to have basic knowledge of methadone and buprenorphine to better engage, counsel, and refer patients seeking treatment.

Buprenorphine is usually prescribed as a film or tablet; however, it is also available as a monthly subcutaneous injection or subdermal implant every 6 months. The sublingual or buccal film and sublingual tablet is usually prescribed at least daily. The films and tablets may be available at 2 mg, 4 mg, and 8 mg doses. They can be prescribed alone or as a combination with naloxone. The naloxone component is added to buprenorphine as a deterrent. Naloxone is poorly absorbed when the buprenorphine-naloxone film or tablet is taken as prescribed. If the medication is manipulated for intravenous or intranasal use, naloxone's opioid antagonist activity takes effect and could cause an acute opioid withdrawal [34].

Buprenorphine is a partial opioid agonist with a high affinity for the mu opioid receptor. It has a long half-life of at least 24 h [34]. Because it is a partial agonist, there is a "ceiling effect." This means once the opioid receptors are saturated, higher doses would be unlikely to cause respiratory depression. This makes the risk of overdose lower compared to methadone.

Methadone is a full-opioid agonist usually taken daily by mouth. Like buprenorphine, it has a long half-life. It reaches its peak effect after about 3–5 days of continuous use [34]. Thus, caution with dose escalation is recommended to prevent overdose.

Both methadone and buprenorphine show equivalent efficacy for opioid withdrawal and maintenance when dosed appropriately [35, 36]. However, there are several major dif-

ferences between buprenorphine and methadone. First, methadone requires more frequent visits compared to buprenorphine. Methadone programs usually require daily attendance for supervised administration while buprenorphine can be given as a monthly prescription. Stable patients may be seen every 3 months based on the prescribing clinician's discretion.

Another major difference is how the medications are started. Buprenorphine is usually initiated once the patient is in opioid withdrawal. This is done to prevent an acute, or precipitated, withdrawal. Rapid-onset, severe opioid withdrawal can occur if buprenorphine is taken when there are already full agonists attached to opioid receptors. Since buprenorphine has stronger receptor binding affinity but weaker effect, withdrawal can occur when it rapidly displaces the other opioids from the receptor.

Buprenorphine is usually initiated at a low dose once the patient is in opioid withdrawal [34]. However, patients who are unable to tolerate withdrawal symptoms can be induced with a different technique in which buprenorphine can be started at extremely low doses while the patient is weaning off another opioid [37]. Methadone does not carry the same risk of induced opioid withdrawal.

The last major difference to highlight is the different risk profiles of these two medications. As referenced above, methadone has a higher risk of overdose. In addition, it is more likely to have drug-drug interactions and QT interval prolongation compared to buprenorphine [34, 38, 39].

Given the differences in visit frequency, induction protocols, and risks, the clinician and patient should engage in shared decision-making when choosing a medication for OUD. This discussion should begin by assessing the patient's preference. There are websites with excellent materials for both clinicians and patients to assist in shared decision-making for opioid use disorder treatment, including the California Health Care Foundation Project SHOUT website: https://www.chcf.org/collection/webinar-series-support-hospital-opioid-use-treatment-project-shout/ [40].

Clinical Pearls

- Primary care providers play an important role in screening, preventing, and treating patients with risky substance use and substance use disorder.
- Screening starts with a question screener. Positive alcohol screens should have a follow-up with the AUDIT. For positive drug screens, follow up with the DAST-10.
- Management depends the patient's risk:
  - No or low risk: brief intervention via counselling.
  - Moderate, high, or severe risky use: referral to therapy or a treatment program.
  - Moderate to severe substance use disorder: medication-assisted treatment, ideally via referral to a treatment program.

Don't Miss This!

- Engage all patients with risky substance use in harm reduction strategies. Give naloxone kits to patients with risky opioid use.
- Substance use care should be patient-centered and non-judgmental. Help patients reach their individual goals instead of focusing solely on abstinence.
- Offer medication for moderate to severe opioid and alcohol use disorder treatment.

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Part II
Endocrine

Chapter 7
Diabetes

Ari Geliebter

Abbreviations

A1C	Hemoglobin A1C
AGIs	Alpha-glucosidase inhibitors
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase 4
GLP-1	Glucagon-like peptide-1
SGLT-2	Sodium-glucose cotransporter-2
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TZD	Thiazolidinediones

Introduction

Diabetes mellitus (DM) is a heterogeneous, complex, and chronic disease in which glycemic regulation and control are progressively lost, leading to hyperglycemia. Diabetes can lead to many adverse short- and long-term consequences for

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patients, and diabetic management is focused on mitigating these adverse outcomes [1]. Studies such as the UKPDS, DCCT, and ACCORD have demonstrated that achieving glycemic control can significantly reduce many DM complications, especially microvascular complications [2–4]. More recently, the introduction of GLP-1 agonists and SGLT2 inhibitors has been shown to potentially improve cardiovascular and renal outcomes in selected patients [5, 6]. A new diagnosis of DM has major ramifications for patients, providers, and the healthcare system overall. Effective management not only includes glycemic management but also management of coexisting conditions such as hypertension and hyperlipidemia. Patients may become overwhelmed by the complexity of DM control and the myriad of recommendations given by their healthcare providers, thus jeopardizing their ability to achieve treatment aims and to impact quality of life. A patient-centered approach remains the foundation for successful management of DM and the prevention of DM-related complications [1].

Much has been written about the high prevalence of DM in the USA. As many as 34.2 million people, or 10.5% of the US population, have diabetes as of 2018, and nearly a quarter of adults are unaware of their diagnosis [7]. Given the great benefit of tight glycemic control early in the disease process, identification and screening high-risk individuals remains a priority.

The majority of patients fall into one of the two categories, type 1 diabetes or type 2 diabetes [8].

- Type 1 diabetes (T1D): an autoimmune disease in which the insulin-producing beta cells are destroyed, leading to an insulin-deficient state. Overall, about 5% of all patients with diabetes have T1D [9]. While the majority of T1D patients are diagnosed at a relatively young age, a new diagnosis of T1D can occur later in life. The rate of beta cell destruction is variable, and patients with T1D may still produce varying amounts of insulin for some time. T1D patients eventually become dependent on exogenous insulin administration to maintain glycemic control.
- Type 2 diabetes (T2D): a disease state in which glycemic control is lost due to a combination of factors, including

insulin resistance and relative insulin insufficiency. Approximately 90–95% of all patients with diabetes have T2D [7]. The average age at diagnosis of T2D is older than of T1D; however T2D has also been increasingly diagnosed in younger ages.

- Other DM types: gestational DM, maturity-onset diabetes of the young (MODY), drug-induced DM, drug or chemical induced diabetes, destruction of the exocrine pancreas from cystic fibrosis or pancreatitis.
- Pre-DM: a state in which patients do not meet criteria for DM, but glucose levels are abnormal. Studies have demonstrated that pre-DM often progresses to overt DM, and thus early intervention is considered important.

Diagnosis of DM

DM is commonly diagnosed based on the following ADA criteria [8]:

1. Fasting plasma glucose of ≥126 mg/dL (fasting for 8 h).
2. A1C ≥ 6.5%.
3. Classic symptoms of hyperglycemia + plasma glucose of ≥200 mg/dL.
4. Two-hour plasma glucose of ≥200 mg/dL after a 75-gram oral glucose load.

Pre-DM is diagnosed with the following ADA criteria [8]:

1. Fasting plasma glucose of 100–125 mg/dl.
2. A1C 5.7–6.4%.
3. Two-hour plasma glucose of 140–199 g/dL after a 75-gram oral glucose load.

A single test is typically insufficient for the diagnosis of DM and should be repeated to confirm the diagnosis.

Distinguishing between T1D and T2D may initially be difficult. A careful history and physical examination may suggest a specific diagnosis, but final confirmation usually occurs over time. While diabetic ketoacidosis (DKA) is often the hallmark of T1D, it can also occur on occasion in some T2D

patients as well. Similarly, while certain characteristics such as obesity and dyslipidemia are more common in T2D patients, they can be encountered in T1D patients and thus cannot be used to definitively classify a disease type. When T1D is suspected, autoimmune markers such as antibodies to islet cells and insulin, GAD65, IA-2 and IA-2β, and ZnT8 can be used to help aid in the diagnosis [8]. Insulin secretion can also be assessed in the ambulatory setting by measuring a C-peptide level in the setting of hyperglycemia, with a low value being more consistent with insulin-deficiency and T1D.

Screening for DM

Given the large number of patients with undiagnosed diabetes, an evidence-based screening program is important.

According to the US Preventive Services Task Force, the following patient populations without obvious diabetes symptoms should be screened in the ambulatory setting [10]:

- Patients aged 35–70 who are overweight (BMI ≥ 25) or obese (BMI ≥ 30).
- Consider earlier screening for overweight or obese patients from a population with a higher prevalence of diabetes, such as American Indians/Alaskan Natives, Blacks, Hispanics/Latinos, or Native Hawaiians/Pacific Islanders.
- Consider earlier screening at BMI ≥ 23 for Asian Americans.

The USPSTF suggests repeat testing of high-risk patients every 3 years [10].

Key H&P in Early DM

The symptoms and signs of DM are often due to the presence of hyperglycemia. The early stages of DM may often be asymptomatic when the hyperglycemia is mild, but a comprehensive history and physical exam might suggest the diagnosis.

History

The classic symptoms of polyuria, polydipsia, and weight loss are consistent with the osmotic diuresis that can accompany hyperglycemia. Additionally, symptoms such as fatigue, malaise, and blurry vision may be present as well. When T1D is suspected, patients should be asked about the presence of any co-existing autoimmune diseases such as vitiligo and primary hypothyroidism.

Physical Exam

There are few exam findings specific to DM. Cutaneous findings such as acanthosis nigricans and skin tags may suggest the presence of insulin resistance.

Healthcare Maintenance in the Patient with Diabetes [11]

- Annual eye exam
- Annual monofilament test or other test for detecting neuropathy
- A1C every 3–6 months depending on control
- Annual lipid panel
- Annual spot urinary albumin-to-creatinine ratio
- Blood pressure at every visit
- Annual influenza vaccine and pneumococcal vaccine at appropriate intervals
- COVID-19 vaccination

Treatment of DM

Effectively treating DM requires a patient-centered approach that includes lifestyle modification, glycemic control, and management of comorbid conditions such as obesity, hyper-

tension, and dyslipidemia. Patients with DM are at significantly increased risk for cardiovascular disease including myocardial infarction and stroke, as well as retinopathy and nephropathy, and mitigating these risks remains a primary goal of DM management and treatment [1].

DM complications can be divided into microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (CV disease) categories. Intensive glycemic control has been associated with significant reductions in microvascular complications in both T1D and T2D and in macrovascular complications in T1D [2–4]. Importantly, while intensive glycemic control has not been consistently found to reduce macrovascular complications in T2D, SGLT2 inhibitors and GLP1 agonists have been shown to mitigate cardiovascular complications in high-risk patients [5, 6]. Additionally, cardiovascular risk can be improved by aggressively addressing the traditional risk factors of hypertension, hyperlipidemia, smoking cessation, and weight loss.

A1C Treatment Goals in DM [12, 13].

- 6–6.5%: for patients who can achieve tight glycemic control without hypoglycemia or other adverse effects of treatment
- <7%: for most nonpregnant patients without significant hypoglycemia
- <8%: for patients with limited life expectancy or where adverse effects of treatment are significant

Type 1 Diabetes

Insulin therapy is required in the management of T1D, and a comprehensive guide to T1D management is beyond the scope of this resource.

Patients with T1D require both basal and prandial insulin administration. Insulin can be administered with multiple daily injections or using an insulin pump (continuous subcutaneous insulin infusion). Prandial insulin should account for the anticipated carbohydrate intake and pre-meal sugars, and

a personalized assessment for prandial insulin requirements is a crucial part in the successful glycemic management in T1D. Self-monitoring of glucose should be performed both pre-meal and post-meal to assess adequacy of the insulin regimen. A continuous glucose monitoring (CGM) has been associated with A1C reductions [14] and is generally considered the standard of care for all patients with type 1 diabetes. The current generation of hybrid closed-loop pump systems has shown promise in reducing hypoglycemia and improving overall glycemic control.

Type 2 Diabetes

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have published comprehensive treatment guidelines for T2D [1, 13]. While there are many different treatment approaches for patients with T2D, it is important that the chosen approach be understood and agreed upon by both patient and provider for the highest chances of success.

Lifestyle Changes

Lifestyle changes remain a backbone of treatment for most patients with T2D as they may partially correct the insulin resistance and impaired insulin secretion associated with the disease. These changes include weight loss, increased physical activity, and smoking cessation. Caloric restriction is a critical aspect of successful weight loss, and nutritional counseling and support with realistic goals can help patients make the appropriate changes to their diet necessary for weight loss [13]. Meal planning for the diabetic patient requires an understanding of the glycemic index of carbohydrate containing foods. Educating patients regarding meal composition and portion size is also essential. Patients should be given a prescription for increased physical activity advising 30–45 min 4–5 times/week of aerobic exercise.

Motivated patients with newly diagnosed DM with an A1C ≤7.5% may be tried on a 3–6-month trial of lifestyle changes alone but should be started on pharmacotherapy if glycemic targets are not reached. In the majority of patients, lifestyle changes alone are insufficient to achieve sustained adequate glycemic management, and pharmacotherapy will be necessary.

Pharmacological Therapy in T2D

Pharmacological therapy is eventually needed in most patients with T2D. Since early achievement of tight glycemic control has been associated with overall improved outcomes, it is imperative that pharmacological therapy adequate to achieve glycemic goals be initiated early in the disease course. There are several pathophysiological defects in T2D, and combination therapies that address several of these defects should be considered in all patients [15].

The choice of therapy should be tailored to fit each patient's individual glycemic goals while balancing the potential adverse effects of therapy including hypoglycemia. In adults with recently diagnosed T2D and without significant comorbidities such as established cardiovascular disease, intensive therapy sufficient to achieve an A1C of 6.0–6.5% should be initiated to reduce microvascular and macrovascular disease [13]. In adults with a longer diabetes course, with established cardiovascular disease or other significant comorbidities, the risk of hypoglycemia and other adverse events associated with the intensive therapy begins to outweigh the potential benefits, and a more lenient A1C target of 7.0–8.0% is appropriate. See Fig. 7.1 for a suggested pharmacological approach to glycemic management in T2D treatment.

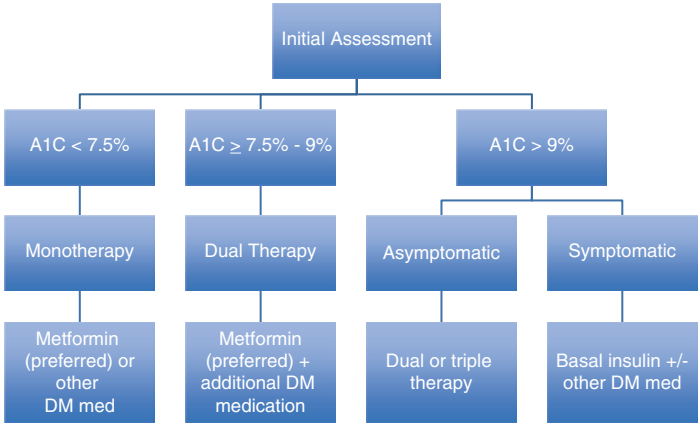

FIGURE 7.1 Initial glycemic management (adapted from the AACE Comprehensive Type 2 Diabetes Management Algorithm, 2020)

Choice of Therapy

Both the American Diabetes Association and the American Association of Clinical Endocrinologists have created comprehensive algorithms for pharmacotherapy in T2D [13, 16]. Below is a summary of commonly available diabetic medications, and is also available in Table 7.1.

Metformin

The exact mechanism of action of metformin remains unclear, but it appears to primarily decrease hepatic glucose production. Metformin has a long-established cardiovascular safety profile, can promote weight loss, and has a low risk of hypoglycemia. Metformin can have a substantial positive impact on glycemic control with doses of 2000–2500 mg daily. For these reasons, metformin is often the initial agent prescribed for patients with T2D and remains the backbone of therapy.

Table 7.1 Commonly used non-insulin diabetic medications

Drug name	Route	Dosage	Timing	Notable side effects
Biguanides (MOA: Decreased hepatic glucose output)				
Metformin IR/metformin XR	Oral	IR: 500–2550 mg XR: 500–2000 mg	IR: 2–3×/day XR: 1–2×/day	GI upset, B12 deficiency, renal dosing, lactic acidosis (rare)
Sulfonylureas/meglitinides (MOA: Increased insulin secretion)				
Glimepiride	Oral	1–8 mg	1–2×/day	Hypoglycemia, weight gain
Glyburide		2.5–20 mg	1–2×/day	
Glipizide IR/glipizide XR		IR: 2.5–20 mg XR: 5–20 mg	IR: 1–2×/day XR: 1×/day	
Repaglinide		0.5–4 mg	With meals	
Nateglinide		60–120 mg		

GLP-1 receptor agonists (MOA: Glucose-dependent insulin release via GLP-1)				
Exenatide IR Exenatide XR	SQ	IR: 5–10 mcg XR: 2 mg	IR: 2×/day XR: Weekly	GI upset
Liraglutide		0.6–1.8 mg	Daily	
Lixisenatide		10–20 mg	Daily	
Dulaglutide		0.75–4.5 mg	Daily	
Semaglutide		0.25–1 mg	Weekly	
Semaglutide	Oral	3–14 mg	Daily	
Dipeptidyl peptidase 4 (DPP-4) inhibitors (MOA: Inhibiting DPP-4, thereby increasing GLP-1)				
Sitagliptin	Oral	25–100 mg	Daily	Well tolerated
Saxagliptin		2.5–5 mg		
Linagliptin		5 mg		
Alogliptin		6.25–25 mg		

(continued)

TABLE 7.1 (continued)

Drug name	Route	Dosage	Timing	Notable side effects
Thiazolidinediones (TZDs) (MOA: Increases insulin sensitivity through binding of PPAR)				
Pioglitazone	Oral	15–45 mg	Daily	Weight gain, edema, possible increase in fractures
Sodium-glucose co-transporter 2 (SGLT-2) inhibitors (MOA: Inhibition of urinary glucose reabsorption)				
Canagliflozin	Oral	100–300 mg	Daily	Vulvovaginal candidiasis, urinary tract infections, hypotension
Ertugliflozin		5–15 mg		
Empagliflozin		10–25 mg		
Dapagliflozin		5–10 mg		
Alpha-glucosidase inhibitors (AGIs) (MOA: Inhibition of carbohydrate absorption)				
Acarbose	Oral	25–100 mg	With meals	GI upset
Miglitol		25–100 mg		

Adverse effects include gastrointestinal effects, B12 deficiency, and the potential for lactic acidosis. GI effects can be minimized with slow-dose titration, administration with foods, and the use of extended-release formulations. B12 deficiency has been associated with metformin use, and B12 levels should be measured in all patients on metformin.

Of note, lactic acidosis is an extremely rare consequence of metformin therapy and is associated with pre-existing renal insufficiency. The new FDA guidelines (2016) recommend that metformin should not be initiated when eGFR drops below 45 mL/minute/1.73 m^2, should be reconsidered in patients already on metformin when eGFR drops below 45 mL/minute/1.73 m^2, and should be stopped completely when eGFR drops below 30 mL/minute/1.73 m^2. Metformin should also be stopped prior to imaging studies with iodinated contrast [17].

Sulfonylureas (Glimepiride, Glyburide, Glipizide) and Meglitinides (Repaglinide, Nateglinide)

Sulfonylureas act by binding to potassium channels on pancreatic beta cells, inducing insulin secretion. Sulfonylureas can significantly improve glycemic control, are available in once-daily formulations, and are often prescribed as add-on therapy to metformin. Dosing should be increased slowly as some patients are prone to becoming hypoglycemic while on sulfonylureas. Sulfonylurea doses need to be adjusted in patients with underlying kidney disease given the overall long duration of action. Glipizide is the preferred sulfonylurea in patients with chronic kidney disease. The meglitinides have a shorter half-life as compared with sulfonylureas, are taken with meals, and may carry a lower risk of hypoglycemia.

Adverse effects include hypoglycemia, lack of durability, and weight gain. Sulfonylureas have a high incidence of hypoglycemia as compared with other non-insulin therapies, and patients should be advised to monitor their glucose while on therapy.

GLP-1 Receptor Agonists (Exenatide, Liraglutide, Dulaglutide, Lixisenatide)

GLP-1 receptor agonists act by binding to glucagon-like peptide-1 receptors and inducing glucose-dependent insulin release from the beta cells. GLP-1 receptor agonists have a strong glycemic effect and are associated with weight loss and blood pressure reductions. Importantly, they have demonstrated significant cardiovascular and renal benefits and are recommended for use in patients with high risk for cardiovascular disease (established atherosclerotic disease, heart failure, established kidney disease). They may be used as add-on therapy to metformin and can often be used as an alternative to basal insulin therapy in selected patients. GLP-1 receptor agonists are available as daily or weekly injectables, and in a daily oral formulation. Exenatide should not be used with eGFR <30 ml/min.

Adverse Effects Gastrointestinal side effects include nausea, vomiting, and diarrhea and may be improve over time and with slow dose titration. GLP-1 receptor agonists should be used with caution in patients with gastroparesis. GLP-1 agonists have also been associated with pancreatitis in some studies and should be used cautiously in patients with a personal history of pancreatitis.

GLP-1 agonists should not be given to patients with a personal or family history of MEN type 2 (multiple endocrine neoplasia) or medullary thyroid cancer.

DPP-4 Inhibitors (Sitagliptin, Saxagliptin, Linagliptin, Alogliptin)

DPP-4 inhibitors act by inhibiting dipeptidyl peptidase 4 (DPP-4), leading to increased levels of GLP-1. DPP-4 inhibitors have modest glycemic effect but are commonly prescribed as they have few adverse effects, are weight neutral, dosed once daily, and are available in combination with met-

formin. DPP-4 inhibitor dosages need to be adjusted in patients with underlying kidney disease except for linagliptin.

Adverse Effects DPP-4 inhibitors have also been associated with pancreatitis in some studies and should be used cautiously in patients with a history of pancreatitis.

SGLT-2 Inhibitors (Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin)

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors block the reabsorption of glucose in the nephron, resulting in an osmotic diuresis. SGLT-2 inhibitors have modest glycemic effects and can decrease weight and systolic blood pressure. SGLT-2 inhibitors as a class have generally been associated with decreased all-cause and CV death, heart failure hospitalizations, and progression of chronic kidney disease. SGLT-2 inhibitor dosages need to be adjusted in patients with underlying kidney disease.

Adverse Effects SGLT-2 inhibitors can lead to dehydration and hypotension. They have been associated with an increased incidence of genital mycotic infections, necrotizing fasciitis of the perineum, bone fractures, and the development of euglycemic ketoacidosis with SGLT-2 inhibitor use.

Thiazolidinediones (Pioglitazone)

TZDs are the only diabetes medication class that directly reduces insulin resistance by binding to peroxisome proliferator-activated receptors, although the exact mechanisms are unknown. Patients with severe insulin resistance may benefit from TZD therapy. TZDs have modest glycemic efficacy, have a durable effect, and have a low risk of hypoglycemia. Pioglitazone may also have a beneficial impact on lipids, as well as on hepatic steatosis.

Adverse Effects TZDs are associated with significant dose-dependent weight gain and edema and should not be used in patients at increased risk for heart failure. TZDs have also been linked to an increased rate of bone fractures as well as a possible association with bladder cancer.

Alpha-Glucosidase Inhibitors (AGIs) (Acarbose, Miglitol)

AGIs act by inhibiting carbohydrate absorption in the small intestine and have a significant dose-dependent impact on post-prandial glucose levels. Acarbose has also been associated with improved CV outcomes in patients with impaired glucose tolerance. AGI doses need to be adjusted in patients with underlying kidney disease.

Adverse Effects AGIs often cause flatulence and diarrhea, which can often be improved with lower doses.

Insulin

Insulin remains a potent and effective treatment to lower blood glucose in the majority of patients and may be the appropriate choice of therapy for selected patients. Long-standing patient with diabetes patients with diabetes already on two non-insulin agents with an A1C > 8% will likely require the addition of insulin to achieve glycemic targets. Additionally, if the A1C is significantly elevated on initial diagnosis (>9–9.5%) and the patient is significantly symptomatic from the hyperglycemia, insulin can be useful to help rapidly lower the A1C and improve symptoms.

Insulin can be given as either a basal dose to help suppress hepatic glucose production, or as a prandial dose to help improve post-prandial spikes in glucose. See Table 7.2 for the time profiles of the commonly prescribed insulin formulations. Generally, basal insulin is initially prescribed and slowly up titrated to achieve normal fasting glycemic levels. Basal insulin can be initiated at a dose of 0.1–0.2 U/kg and should be slowly titrated every 2–3 days in order to achieve a fasting

Table 7.2 Common insulin formulations [18]

Long-acting	Onset	Peak effect	Duration (h)
Degludec U-100/U-200	1–2 h	None	>40
Detemir	1–2 h	None	14–24
Glargine U-100/U-300	3–6 h	None	24
Intermediate-acting			
NPH	1–2 h	4–12 h	18–26
Rapid-acting			
Regular U-100	30–60 min	2–4 h	6–8
Lispro/aspart/glulisine	5–15 min	40–75 min	3–5
Lispro-aabc	<10 min	1–2 hours	4–6

blood glucose of <130 mg/dL. Some patients with significant insulin resistance may require very high doses of insulin in order to achieve their glycemic targets. Prandial insulin should be considered once the basal insulin dose is greater than 0.5 U/kg, with the goal of lowering a 2-hour postprandial glucose of <180 mg/dL. Of note, multiple injections of insulin daily may impose a significant burden on patients and should be carefully considered before initiation.

When insulin is prescribed, patients should be educated carefully about administration techniques, timing, and consistency of dosing and the proper use of blood glucose monitoring with a glucometer. Hypoglycemia remains a primary concern with insulin use given its association with significant comorbidity, and patients should be educated about the symptoms and management of hypoglycemia.

Clinical Pearls

- Diabetes mellitus is an increasingly common diagnosis in the USA and should be considered in patients with polyuria, polydipsia, and fatigue.
- Diagnosis of DM can be made in the office if fasting plasma glucose is >126 mg/dl or if plasma glucose is >200 mg/dl with hyperglycemic symptoms.

- Screening for diabetes is indicated for individuals at high risk for diabetes including patients who are 35–70 years old and overweight or obese.
- Given the many treatment options available in T2D, patients and providers should be in agreement about glycemic aims before a new regimen is initiated.
- SGLT2 inhibitors and GLP1 agonists have been demonstrated to improve cardiovascular and renal outcomes in selected patients.
- Insulin therapy is ultimately required in many patients with T2D.

Don't Miss This!

- Diabetes mellitus is a chronic and complicated disease, and successful management can often be overwhelming for patients and lead to poor medication adherence. When assessing a potential treatment failure, don't forget to carefully assess for adherence before changing the DM regimen!

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Chapter 8
Thyroid Dysfunction

Nancy A. LaVine

Hypothyroidism

Brief Introduction

Hypothyroidism (both overt and subclinical) is one the most common endocrine disorders, with a prevalence of 1.9% in women and 0.1% in men [1, 2]. Prevalence increases with age in men (0.5%) and women (5.0%) over 60. Treatment of hypothyroidism is with levothyroxine, which accounted for over $3.2 billion in 2016 [3].

The hallmark of hypothyroidism is the insufficient production of thyroid hormones. This can be of a primary nature (under activity of the thyroid gland itself) or of a secondary nature, in which the stimulation of the thyroid gland by the pituitary or hypothalamic glands is inadequate. Primary hypothyroidism accounts for the vast majority (>95%) of hypothyroidism cases. In iodine-sufficient parts of the world, Hashimoto's autoimmune thyroiditis is the most common

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cause of hypothyroidism, while iodine deficiency remains an important cause worldwide [4].

Significant causes of hypothyroidism are listed below.

- Autoimmune thyroiditis
- Severe iodine deficiency
- Non-autoimmune thyroiditis (subacute, silent, and postpartum)
- Partial or total thyroidectomy or other neck surgery
- Thyroid ablation with radioactive iodine therapy
- External radiation to the head and neck
- Infiltrative diseases of the thyroid (amyloidosis, sarcoidosis, hemochromatosis)
- Congenital
- Secondary hypothyroidism (pituitary adenomas, empty sella, pituitary surgery, extra pituitary tumors, inflammatory, or infiltrative diseases)
- Drugs: amiodarone, lithium, interferon, methimazole, propylthiouracil, iodine, iodinated contrast agents

Key H&P

The presentation of hypothyroidism can range from completely asymptomatic to extreme, as symptoms may be influenced by the duration and severity of disease as well as the age of the patient and their sensitivity to thyroid deficiency. Symptoms can be as minor as mild fatigue, cold intolerance, constipation, or weight gain, or, in rare cases, as significant as myxedema coma (hypothermia, coma, pleural, and pericardial effusions). The positive predictive values of varied symptoms of hypothyroidism have been as low as 8–12% in one study [5]. Patients presenting with newly developed symptoms are more likely to have hypothyroidism [6]. Physical exam findings of hypothyroidism can include goiter, bradycardia, or delayed deep tendon reflexes. Given the unreliability of history and lack of physical exam findings, the diagnosis of hypothyroidism in adults is made on the basis of biochemical testing. In addition to those patients presenting

with symptoms, there are certain groups of patients at higher risk for developing hypothyroidism who may need testing:

- Personal or family history of autoimmune thyroid disorders
- Autoimmune endocrine disorders (DMI, adrenal insufficiency, ovarian failure)
- Autoimmune disorders (celiac disease, vitiligo, pernicious anemia)
- Postpartum women
- Treatment of thyroid, pituitary, or hypothalamic glands in the past
- Radiation to the head and neck
- Turner's syndrome
- Down syndrome

Decision-Making/Diagnosis

Thyroid-stimulating hormone (TSH) is the first-line test in the diagnosis of thyroid hormone insufficiency, with a 99% sensitivity and specificity [7]. An elevated TSH with a decreased free T4 (FT4) level is the hallmark of primary hypothyroidism. FT4 alone is less sensitive in detection, and free T3 levels may not be abnormal unless there is severe hypothyroidism. The degree of TSH elevation and the level of free T4 can help further characterize primary hypothyroidism. Patients with overt hypothyroidism will often have a TSH level greater than 10 mU/L with a FT4 below reference range. For some patients, TSH may be mildly elevated (5–10 mU/L) with a low-serum FT4. Other patients may have a milder elevation in TSH (between 5 and 10 mU/L) with a FT4 in the normal range—this is subclinical (or mild) hypothyroidism. The distinction between these categories has important implications for treatment. Of note, some substances can interfere with TSH measurement, including biotin, a commonly used over the counter supplement, which may falsely lower TSH values [8]. Patients taking 10 mg or more of biotin should hold the supplement for 2 days prior to testing.

Treatment

Overt Hypothyroidism

There is strong evidence to support treating patients with overt hypothyroidism (TSH > 10 mU/L) with levothyroxine (LT4) monotherapy. Treatment is generally lifelong, and as such, a confirmatory TSH should be checked prior to initiating therapy. Adequate treatment often improves symptoms, as well as prevents progression of disease and decreases the risk of cardiovascular events. Untreated overt hypothyroidism can result in coronary artery disease, atherosclerosis, heart failure, arrhythmias, and pericardial and pleural effusions, secondary to effects on lipid profiles, the vascular system, and cardiac function [9]. The goal of treatment is to avoid such complications and restore the euthyroid state. Levothyroxine doses should be titrated to normalize the TSH within the reference range. Initial dosing can be based on weight, with a dose of 1.6–1.8 μg/kg/day sufficient to reach a euthyroid state in most patients [10, 11]. Alternatively, a dose of 25–50 μg daily can be started and titrated up. In general, older patients (>60 years old) and those patients with ischemic heart disease should be started at lower doses (25–50 μg) and titrated up over 3–6 weeks.

Monitoring of the TSH level is the most sensitive way to ensure adequate doses of levothyroxine therapy, with monitoring every 4–8 weeks between dosage changes. Patients who have reached a euthyroid state should have TSH monitored every 6–12 months to ensure stability.

Subclinical Hypothyroidism

Patients with subclinical hypothyroidism (an elevated TSH < 10 and a normal FT4) are largely asymptomatic. These patients do have an elevated risk of developing overt hypothyroidism, and several factors have been shown to increase the risk, including the level of TSH elevation and the presence of thyroid peroxidase (TPO) antibodies [12]. Treatment

of subclinical hypothyroidism with levothyroxine remains controversial and is not typically recommended for patients with a TSH < 10. For patients with a TSH ≥ 10, treatment is recommended [13]. Older adults with subclinical hypothyroidism do not appear to benefit from levothyroxine replacement, particularly with a TSH < 10 [14]. Patients with subclinical hypothyroidism should be monitored yearly for continued TSH elevation, the development of overt hypothyroidism, or the development of TPO antibodies (Fig. 8.1).

Treatment Challenges

Levothyroxine absorption and metabolism can be affected by numerous other medications and dietary intake. Both iron and calcium supplements can interfere with absorption. Optimal absorption occurs with fasting, and patients should be advised to take the medication on an empty stomach. Timing of new medication administration should be carefully considered. In a patient with inadequate TSH levels on an optimum weight-based dose, nonadherence (both with the medication and with fasting) as well as absorption problems (such as in celiac disease or previous GI surgeries) should be considered.

Clinical Pearls

- Clinical symptoms have low positive predictive value in the diagnosis of hypothyroidism.
- Thyroid-stimulating hormone (TSH) is the first-line test in the diagnosis of thyroid hormone insufficiency, with a 99% sensitivity and specificity.
- Monitoring TSH alone in patients on levothyroxine replacement is adequate to ensure appropriate dosages.

Don't Miss This!

- Consider nutritional and medication interactions with levothyroxine in patients with elevated TSH despite seemingly adequate levothyroxine dosing.

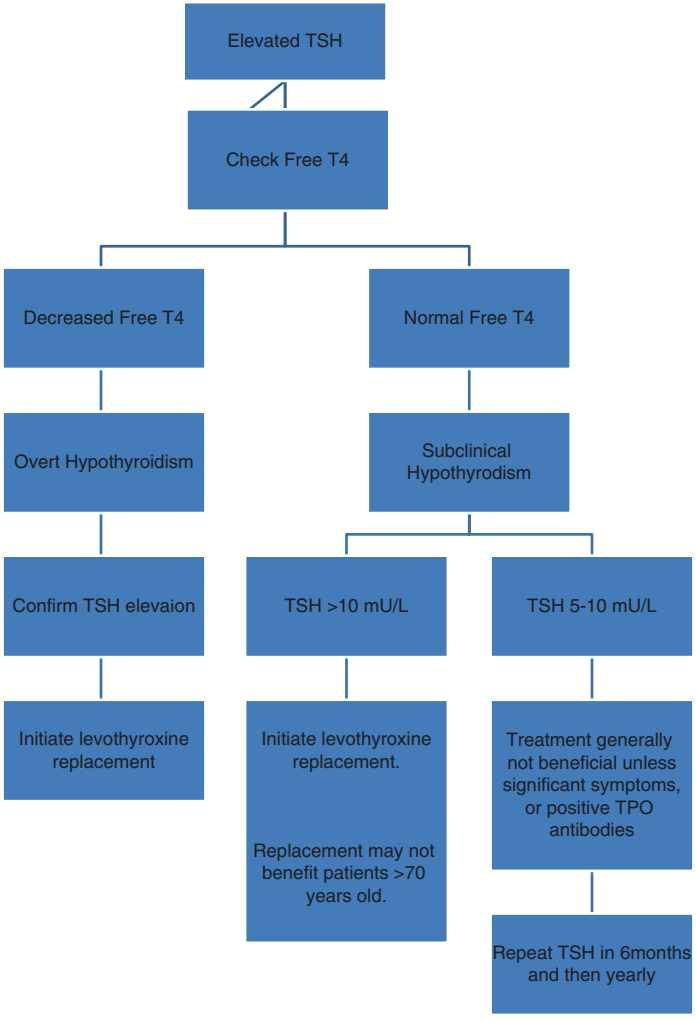

FIGURE 8.1 Treatment algorithm for hypothyroidism

Hyperthyroidism

Brief Introduction

Hyperthyroidism is increased thyroid hormone synthesis and secretion. Thyrotoxicosis is the clinical syndrome of increased circulating thyroid hormone. Hyperthyroidism is found in approximately 1.3% of the US population (0.5% clinical and 0.7% subclinical) [15]. Hyperthyroidism can be overt or subclinical and both will be discussed in this section. The hallmark of hyperthyroidism is the detection of a low level of thyroid-stimulating hormone (TSH) and elevated levels of T4 and/or T3. Subclinical hyperthyroidism is characterized by low-serum TSH and normal levels of T3 and T4 and can be endogenous (due to Graves' disease, toxic multinodular goiter) or exogenous, from excessive intake of thyroid agents (levothyroxine or desiccated thyroid) [16].

Key H&P

Symptoms of overt hypothyroidism can vary, with some of the more prevalent symptoms including fatigue, weight loss, tremulousness/palpitations, anxiety, and heat intolerance. Physical exam findings can include tachycardia, palpable goiter, tremor, and proptosis, and in rare cases, patients can present with thyroid storm (tachycardia, agitation, fever, and altered mental state).

Decision-Making/Differential Diagnosis

Graves' disease, caused by auto-antibodies stimulating the TSH receptor, is the most common etiology of hyperthyroidism, with 3% of women and 0.5% of men developing Graves' disease in their lifetime [17]. Other important etiologies of hypothyroidism include thyroiditis (subacute, silent, or postpartum), which leads to the release of pre-formed thyroid hormone due to

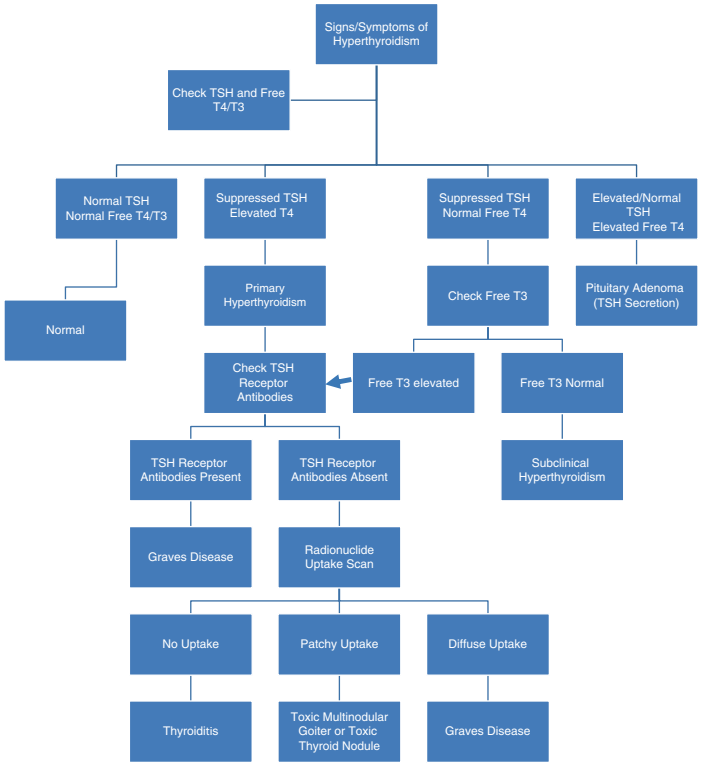

FIGURE 8.2 Diagnostic algorithm for hyperthyroidism

destruction of the thyroid follicles, and toxic nodular goiter, which is more common in iodine deficient areas. The following algorithm outlines a diagnostic workup for diagnosis of the more common etiologies of hyperthyroidism (Fig. 8.2).

Treatment

Graves' Disease

The treatment options for Graves' disease include radioactive iodine (RAI) ablation, antithyroid drugs, and surgical removal

of the thyroid. In the USA, RAI is general favored for initial treatment (58.6%) followed by 40.5% of endocrinologists opting for antithyroid drugs, and only a small minority (1%) recommending surgical therapy [18], though there has been an increase in the use of antithyroid drugs as first-line therapy [19]. Beta blockade is important to minimize clinical symptoms such as palpitations and tremulousness, while other treatments to lower thyroid hormone levels are undertaken. Propranolol, atenolol, and metoprolol are commonly prescribed. Of note, the treatment for toxic nodular goiter or toxic adenoma generally follows that for Graves' disease.

Antithyroid drugs include methimazole and propylthiouracil (PTU). The use of these medications for 12–18 months results in remission in 40–50% of patients [20]. Both of these medications decrease hormone synthesis by interfering with thyroid peroxidase (TPO). Methimazole is the preferred primary treatment for most patients, as PTU has been associated with hepatotoxicity. PTU is utilized in the first trimester of pregnancy and in patients intolerant of methimazole. The starting dose of methimazole is 10–30 mg a day, generally in a single dose, and thyroid function tests are performed within 2–6 weeks. The duration of therapy is approximately 12–18 months, followed by a taper if the patient is felt to be in remission. Adverse effects of the antithyroid drugs include pruritic rash and arthralgias (5%). Agranulocytosis occurs in 1 in 500 patients [21] and typically presents with fever and pharyngitis. Patients taking antithyroid drugs should be warned about this potential side effect. Checking routine white blood cell counts is controversial, though roughly 50% of prescribers routinely check CBCs on patients on thyroid medications [18].

Radioactive Iodine (RAI)

The goal of RAI is to render the patient hypothyroid. RAI is incorporated into thyroid hormone, which causes damage to follicular cells and eventual destruction of the thyroid gland. Most patients develop hypothyroidism 2–3 months after a

single dose of RAI is administered. Serial thyroid hormone measurements should be done at 2–6 week intervals and levothyroxine therapy initiated with free T4 levels drop below normal range.

Surgery

Indications for surgery include large goiters with compressive symptoms, suspicious thyroid nodules, and hyperparathyroidism [22].

Treatment: Subclinical Hyperthyroidism

The need for treatment in subclinical hyperthyroidism is controversial but may be advised in patients with persistently suppressed TSH (<0.10), the elderly, or those with cardiac disease, particularly since the risk of atrial fibrillation is higher in these groups.

Clinical Pearls

- Graves' disease is the most common cause of hyperthyroidism, accounting for 75% of cases, and is mediated by antibodies to the thyroid-stimulating hormone (TSH) receptor.
- Older patients tend to have fewer symptoms of hyperthyroidism.
- Consider treatment of subclinical hyperthyroidism in patients over the age of 65 with persistently suppressed TSH and cardiac history.

Don't Miss This!

- Agranulocytosis occurs in roughly 1/500 patients treated with antithyroid medications, and patients should be alerted to the signs and symptoms of this side effect (fever, sore throat, oral ulcers).
- In older patients, TSH should be measured in the setting of new-onset atrial fibrillation.

Thyroid Nodules

Brief Introduction

The identification of thyroid nodules can occur by several means. The patient may note a change in the neck, or a clinician may identify a nodule on physical exam. Additionally, thyroid nodules may be noted incidentally when patients undergo imaging (ultrasound, CT scanning, etc.) for other reasons. Palpable thyroid nodules are found in 4–7% of the population [23], whereas ultrasound may detect nodules in 19–68% of a random population sample [24]. Workup of thyroid nodules is important to exclude thyroid malignancy, which can occur in 7–15% of thyroid nodules [25].

Key H&P

Thyroid nodules are often asymptomatic. Important history to note in a patient with a thyroid nodule includes history of radiation treatment to the head or neck, family history of thyroid cancers, neck discomfort, rapid growth of the nodule, dysphagia, and hoarseness. Exam should focus on the thyroid, with special attention to the adjacent lymph nodes of the neck.

Decision-Making/Differential Diagnosis

The presence of a nodule on exam should be further evaluated with ultrasonography of the neck and a serum TSH [23, 25]. If the TSH is below normal (suggesting hyperthyroidism), the nodule should be assessed for hyperfunctioning with a radioiodine scan. Hyperfunctioning nodules are rarely malignant, and further workup would include a free thyroxine level and treatment for hyperthyroidism as appropriate. If the nodule is nonfunctional, the characteristics of the nodule will

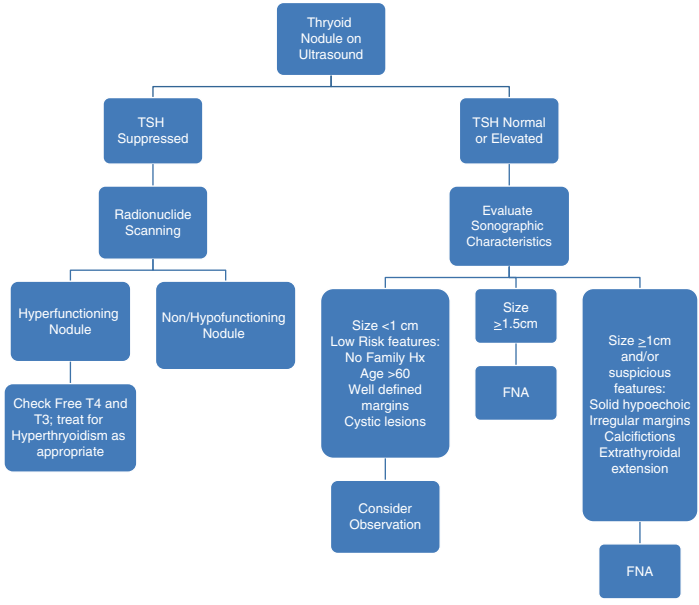

Figure 8.3 Diagnostic algorithm for thyroid nodules

dictate further workup, including possible fine-needle aspiration (FNA). If the TSH is normal or elevated, the characteristics of the nodule will influence further workup (Fig. 8.3).

Treatment

If FNA is performed, further testing and diagnosis will be dependent on the results and may include observation or surgical thyroidectomy [25].

Clinical Pearls

- Thyroid nodules are common in the general population, though most are benign.
- Thyroid ultrasound and TSH measurement are the main factors in guiding diagnosis of thyroid nodules.

Don't Miss This!

- Ultrasound characteristics of suspicious thyroid nodules include: solid hypoechoic nodules with irregular margins, microcalcifications, abnormal cervical lymph nodes, and extra-thyroidal extension.

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Chapter 9
Lipids

Anjali Manavalan

Introduction

Hyperlipidemia encompasses a group of conditions characterized by an increase in serum total or low-density lipoprotein (LDL) cholesterol or triglycerides (TGL). When this occurs due to genetic defects in lipid metabolism, it is called primary hyperlipidemia [1]. However, it may also occur secondary to other diseases—such as diabetes mellitus, HIV, nephrotic syndrome, hypothyroidism, obesity, and other endocrine disorders, or due to lifestyle factors such as smoking, alcohol use, and inactivity. Hyperlipidemia is a well-studied and important risk factor for atherosclerotic cardiovascular disease (ASCVD) [2], which is the leading cause of death not only in the United States but also worldwide [3]. Screening and treating hyperlipidemia for primary and secondary prevention of cardiovascular disease are extremely important in primary care practice.

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Key History and Physical

History

Lipid disorders are usually asymptomatic. The history is focused on the patient's other medical conditions, family history, lifestyle, and risks of cardiovascular disease, all of which can help inform treatment decisions.

Medical History

A review of the patient's medical history is critical to identify possible medical conditions or risk factors that could lead to hyperlipidemia and to estimate the risk for ASCVD. Personal histories of hypertension, diabetes, obesity, cardiovascular disease (CVD), or peripheral vascular disease (PVD) are risk factors that warrant further screening for lipid disorders, according to the USPSTF guidelines (see Decision-Making session for further details).

Family History

A complete family history of chronic metabolic diseases including diabetes, lipid disorders, and cardiovascular disease should be obtained. Early-onset cardiovascular disease in first-degree family members is an important risk factor for ASCVD and should also be ascertained.

Social History

A complete history of the patient's dietary habits, physical activities, and alcohol and tobacco use should be evaluated. They are parameters to evaluate a patient's risk of lipid disorders, metabolic syndrome, and cardiovascular events. In

addition, these factors are also significant points of possible intervention after establishing the clinical diagnosis of hyperlipidemia (see Treatment Strategies session for details).

Physical Exam

In most patients there is no specific physical exam for lipid disorder. Xanthomas are circumscribed plaque or nodule-like lesions in the skin, tendons, or fasciae and could be seen occasionally in patients with primary or secondary hyperlipidemia. They are derived from macrophages containing a high amount of LDL particles [4]. Xanthelasma are soft, yellow plaques that are usually symmetric and occur on the medial aspect of the eyelids. These are also associated with disorders of LDL metabolism. On the other hand, physical exam might reveal signs of atherosclerotic vascular diseases, such as carotid bruits, cardiac murmurs due to aortic valve atherosclerosis, renal artery bruits due to atherosclerotic stenosis, and signs of peripheral vascular disease (e.g., diminished pulses; cold, dry, and shiny skin; ulceration or gangrene; etc.). In addition, the presence of obesity or acanthosis nigricans should prompt further evaluation for dyslipidemia.

Decision-Making/Differential Diagnosis

Screening Population

The US Preventive Services Task Force (USPSTF) strongly recommends screening for lipid disorders in men ≥35 years of age and women ≥45 years of age (Grade A recommendation). The screening is also recommended in men of age 20–35 and women of age 20–45, with increased risks for cardiovascular disease (Grade B recommendation). The risk factors for CVD include hypertension, diabetes, obesity (BMI ≥ 30), tobacco use, family history of early-onset CVD (onset before

age 55 in male or age 65 in female first-degree relatives), and personal history of CVD or noncoronary atherosclerosis (e.g., abdominal aortic aneurysm, peripheral artery disease, carotid artery stenosis, etc.).

USPSTF recommends screening for lipid disorders every 5 years and with shorter intervals for patients with lipid values that are close to warranting therapy.

Testing Lipid Levels: Fasting vs. Non-fasting

Current guidelines recommend that the lipid panel should be tested while fasting, i.e., 8–12 h of complete diet restriction, in order to ensure the accuracy and prevent effects of meals on lipid parameters [5]. In most clinical laboratories, the LDL-c level is calculated by the Friedewald formula (LDL-c = total cholesterol − HDL-c − [triglycerides/5]) using fasting samples. The assumption is that the VLDL-c level can be estimated by the level of triglycerides, which, however, is impacted by the non-fasting state. The calculated LDL-c level might be inaccurate in individuals with high triglycerides or low LDL-c levels [6].

However, a fasting test may be inconvenient in clinical practice and might delay clinical evaluation. Comparisons between fasting and non-fasting studies have shown that other than triglyceride levels which are impacted by non-fasting status, other lipid parameters such as total cholesterol and HDL-c vary little in the general population [7]. Also, non-fasting LDL-c (calculated) has a similar prognostic value as fasting LDL-c [8]. Therefore, acquiring a non-fasting lipid panel test has been suggested for screening.

Assessing Risk for ASCVD

The 2019 ACC/AHA guidelines recommend calculating 10-year ASCVD risk and lifetime risk for individuals between the ages of 40 and 79. This can be performed using the

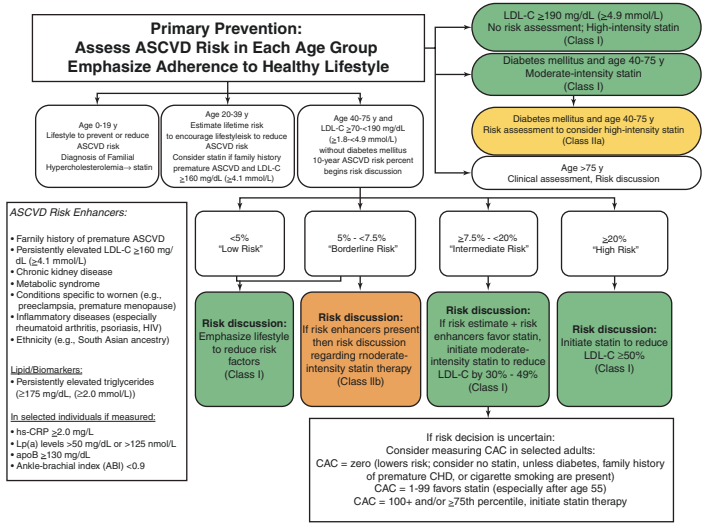

FIGURE 9.1 Algorithm for cholesterol management in primary prevention recommended by the ACC/AHA guidelines

ASCVD risk calculator [9]. This calculator is based on observational data from the Framingham Study and additional studies on predominantly non-Hispanic white and non-Hispanic black residents of the United States. This tool may over- or underestimate risk in other race/ethnic groups or non-US populations, particularly in those of South Asian ancestry. In those individuals with low to intermediate risk for ASCVD, the presence of risk enhancers should be considered when making decisions about initiating lipid-lowering therapy (Fig. 9.1).

Treatment

In 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) released updated guidelines for cholesterol management in primary prevention [10].

Instead of targeting LDL-level goals, which was recommended by the previous Adult Treatment Panel (ATP) III guidelines [11], the ACC/AHA guidelines promote lipid-lowering strategies depending on the ASCVD risk for primary prevention [9, 10]. This recommendation has been upheld in the ACC/AHA 2019 guidelines for lipid-lowering therapy in primary prevention [9].

Principles of Therapy

In the 2019 ACC/AHA guidelines, the initiation and dosage of lipid lowering therapy in *primary prevention* is dependent on a patient's 10-year ASCVD risk (Fig. 9.1). Patients 20–39 years of age are considered to be at low risk for cardiovascular events but may be candidates for statin therapy based on the presence of risk enhancers such as abnormal ABI/PVR, elevated coronary artery calcium score, family history, and high-sensitivity CRP, to name a few [12–15]. Statin therapy may be considered in younger individuals who have had type 1 diabetes for a duration longer than 20 years or type 2 diabetes for longer than 10 years. In those individuals with borderline ASCVD risk, coronary artery calcium score can assist with reassessing risk. The benefit of initiating statin therapy in those older than 75 years is not clear and should take into account the individual clinical scenario.

All patients with established clinical ASCVD should be initiated on statin therapy for *secondary prevention*. High-intensity statin with a goal to lower LDL-C levels to less than 70 mg/dL is indicated for patients 76 years of age and younger as this has been shown to decrease cardiovascular events. If there is intolerance to statin therapy or the target LDL-C remains unmet, the addition of other agents (ezetimibe, PCSK9) is recommended to meet the LDL-C goal [9].

Treatment Strategies

Lifestyle Modification

Lifestyle modification remains a critical part of cholesterol management in the AHA guidelines. Lifestyle modifications include adhering to a healthy diet, regular exercise, abstinence to tobacco products, and controlling body weight [9].

Certain diets such as the DASH diet lower blood pressure and LDL-c and have been shown to lower LDL-c by 11 mg/dL in adults with LDL-c levels <160 mg/dL (high strength of evidence) [11]. Further, reducing calories from saturated fat and trans-fat has been shown to lower LDL-c [11]. In general, it is recommended that all adults consume a healthy plant based or Mediterranean diet high in vegetables, fruits, nuts, whole grains, lean vegetable or animal protein such as fish, and vegetable fiber which has shown to decrease all-cause mortality compared to standard diets.

Evidence shows that both aerobic physical activity and resistance training reduce LDL-c and non-HDL-c levels. Comparing with controls, aerobic physical activity lowers LDL-c by 3–6 mg/dL and non-HDL-c by 6 mg/dL (moderate strength of evidence); resistance training reduces LDL-c and non-HDL-c by 6–9 mg/dL (low strength of evidence) [11]. The 2019 ACC lifestyle guideline recommends engaging in 150 min of moderate-intensity physical activity or 75 min of vigorous-intensity physical activity per week to decrease the risk of ASCVD [9].

Statins

Statins are the cornerstone and first-line lipid-lowering therapy. Statins act by inhibiting hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme in cholesterol biosynthesis. This subsequently leads to upregulation of the LDL receptor, increased LDL uptake, and reduction of serum LDL-c [16].

Table 9.1 Suggested statin and dose for the appropriate intensity of therapy

Statin intensities		
High-intensity (lower LDL-c > 50%)	**Moderate-intensity (lower LDL-c 30–49%)**	**Low-intensity (lower LDL-c < 30%)**
Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin 80 mg Pitavastatin 1–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

The type and dose of statin determine their potential for LDL-c reduction. Low-intensity statin therapy reduces LDL-c by less than 30%; moderate-intensity statins lower LDL-c by 30–49% on average; and high-intensity statins achieve LDL-c reduction by more than 50% [ACC 2019 guidelines]. Table 9.1 shows the various options of statins and dosages to achieve the targeted intensity of statin therapy.

Statin-associated muscle symptoms (SAMS, including muscle pain and aching, cramps, and weakness) are the most commonly reported adverse effects of statins. The incidence has been estimated to be about 10% [17]. However, a meta-analysis of multiple RCTs showed no difference in the incidence of muscle-related symptoms between statin-treated groups and placebo groups, suggesting the muscle symptoms might not be attributed to statins in many cases [18]. SAMS are usually manifested by pain and weakness of the large muscle groups such as the bilateral thighs, buttocks, back, and shoulders; cramping usually occurs unilaterally in small muscles of hands and feet [19]. SAMS often occur early after starting statin or after increasing the statin dose and generally resolve within 2 months after discontinuation of the medication. Searching for contributing factors (e.g., drug interactions, alcohol use, untreated hypothyroidism, vitamin D

deficiency, etc.), discussion with the patient about the benefits of statin therapy, reassurance, and trial of alternative statins or reduced dosages are suggested in this scenario [19].

Statin therapy may be associated with elevation of transaminase levels, which, however, is not indicative of liver injury in the absence of bilirubin level increase [20]. In many cases the elevations resolve with continuation of statin therapy. Significant liver injury is extremely uncommon with statin use [20]. Routine tests of liver enzymes and liver function are not indicated following statin therapy [20].

Statin use mildly increases the risk of new-onset diabetes (odds ratio 1.12, 95% confidence interval: 1.06–1.18 in the meta-analysis) [21], but the cardiovascular protective effect of statins far outweighs this risk in the majority of cases.

Fibrates

By activating peroxisome proliferator-activated receptor-α (PPAR-α), fibrates primarily decrease triglycerides and raise HDL-c levels. They are commonly used to treat dyslipidemia with elevated triglycerides, when triglyceride levels exceed 500 mg/dL. In the follow-up of the ACCORD Lipid Trial participants, it was noted that the use of fenofibrate resulted in a decrease in cardiovascular events in men with diabetes and triglycerides >204 mg/dL and HDL-c <34 mg/dL, while use in women led to slightly increased risk of both myocardial infarction and stroke (HR 0.84 vs. 1.3) [22]. While these results remain unexplained, it is thought to be due to the smaller number of female participants in the ACCORD Trials as well as a lower rate of events in the placebo group. While no sex differences were noted in participants of the FIELD study, no significant decrease in cardiovascular events were noted in the fenofibrate arm, possibly due to a high rate of statin use among the placebo group [23]. A recent systematic review and meta-analysis comparing statins and fibrate monotherapy revealed no difference in cardiovascular events in both groups with less serious side effects in the statin

group. However, most of the 19 eligible randomized trials included were designed to assess short-term lipid outcomes, making it difficult to be certain about comparisons for long-term outcomes [24].

Fish Oil

Omega 3 fatty acids are valuable adjuncts in decreasing serum triglyceride levels. Icosapent ethyl (Vascepa), when added to statin therapy in patients with elevated triglycerides who suffered from diabetes mellitus or established cardiovascular disease, had a 25% risk reduction in major adverse cardiovascular events [25]. Vascepa was FDA approved in 2019 as adjunctive therapy to statins for individuals with clinical ASCVD or diabetes with two risk factors who have a triglyceride level >150 mg/dL and <500 mg/dL.

Other Non-statin Medications

The 2019 ACC expert consensus documents recommend non-statin therapies in adjunct to statin therapy in patients with clinical ASCVD who have suboptimal LDL-c lowering after lifestyle modification and maximally tolerated statin therapy [9]. The potential adjunctive therapy options include ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK 9) inhibitors [9].

Ezetimibe: Ezetimibe selectively inhibits cholesterol absorption in the small intestine. In combination with maximally tolerated statins, ezetimibe has been shown to produce an additional 24% reduction of LDL. Ezetimibe in combination with statin therapy also significantly reduced ASCVD events (13% reduction in myocardial infarction, 21% reduction in ischemic stroke, and 10% reduction in death from cardiovascular causes) in patients with established ASCD [26].

Bile acid sequestrants: Bile acid sequestrants (BAS) act by binding to bile constituents and disrupting enterohepatic circulation of bile acids. This subsequently leads to increased bile acid production and intrahepatic cholesterol flux, result-

ing in upregulation of LDL receptors, and reduction of LDL-c level. Bile acid sequestrants might be considered as adjunctive therapy if a patient is intolerant of ezetimibe and has a triglyceride level >300 mg/dL. However, the effect of BAS on ASCVD risk reduction remains unclear [27].

PCSK 9 inhibitors: PCSK 9 is a serine protease that binds to the hepatocyte LDL receptor and facilitates its degradation. Inhibition of PCSK 9 therefore increases hepatocyte LDL receptors by preventing their degradation. This enhances hepatic LDL uptake and decreases LDL-c levels. Monoclonal antibodies to PCSK 9, evolocumab and alirocumab, have been shown to lower LDL-c levels by 50–70% from baseline. When used on a background of statin therapy, they significantly reduce the risk of cardiovascular events by 15–20% [28, 29]. Both these drugs were approved by the US Food and Drug Administration (FDA) in 2015 for the treatment of familial hypercholesterolemia and for secondary prevention in patients with established ASCVD and inadequate response or intolerance to statin monotherapy. Inclisiran, a long-acting RNA interference (RNAi) agent that inhibits PCSK 9 protein synthesis, has been noted to decrease LDL levels by 50% on the background of statin therapy in phase 3 trials; however, the number of cardiovascular events was too small to draw meaningful conclusions with regard to ACSVD risk reduction and cardiovascular outcome trials are ongoing [30]. The FDA recently approved the use of inclisiran as add-on therapy to statins in eligible patients. The main side effects related to PCSK9 inhibitor use are related to injection site reactions. New-onset diabetes and nasopharyngitis are also known to occur.

Bempedoic acid: Bempedoic acid is a pro-drug that is activated in the liver to inhibit ATP-citrate lyase. This enzyme lies upstream from HMG CoA reductase; its inhibition results in decrease in cholesterol synthesis in hepatocytes. However, this drug remains inactive in skeletal muscle and is not associated with myopathy. In a recent clinical trial, the addition of bempedoic acid on the background of statin or ezetimibe therapy resulted in 14% reduction in LDLc levels [31]. Cardiovascular outcome data is not yet available. While

there are no specific contraindications to therapy, side effects include uricemia and gout, and this may be exacerbated in those with preexisting disease.

Monitoring After Initiating Therapy

The current ACC/AHA guidelines recommend repeating the lipid panel 4–12 weeks after starting statin therapy or adjusting statin dose and every 3–12 months thereafter, in order to monitor adherence and response to statin therapy [9].

Clinical Pearls

- Hyperlipidemia, or dyslipidemia, is defined as increased levels of lipids, including cholesterol and triglycerides.
- USPSTF strongly recommends screening for lipid disorders in men ≥35 years of age and women ≥45 years of age. Screening is also recommended in men between the ages of 20 and 35 or women aged 20 and 45 with multiple risk factors for atherosclerotic cardiovascular disease.
- Statins remain the first-line therapy for hyperlipidemia, reducing the level of LDL-c and cardiovascular events.
- Four groups were identified to benefit from lipid lowering therapy: patients with clinical ASCVD, patients with LDL-c ≥190 mg/dL, patients between the ages of 40 and 75 with type 1 or type 2 diabetes, and patients with a calculated 10-year ASCVD risk ≥7.5%.
- The ACC/AHA recommends that the intensity of lipid management be tailored to the individual's 10-year ASCVD risk.
- For those individuals with established ASCVD, LDL-C goal of <70 mg/dL is recommended through the use of high-intensity statin monotherapy or in combination with other lipid lowering agents.

Don't Miss This!

- SAMs can occur in about 10% of patients.
- Be familiar with new effective drugs, including PCSK 9 inhibitors, Vascepa, and Bempedoic acid.

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Chapter 10
Obesity

Jacinth S. Ruddock and Gayotri Goswami

Introduction

Obesity is a chronic, relapsing, multifactorial, neurobehavioral disease, where an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass resulting in adverse metabolic, biomechanical, and psychosocial health consequences [1]. Obesity is defined as having a body mass index (BMI) of ≥30 kg/m^2. It is estimated that about 42.5% of the US population are obese, and almost 10% of the country are severely obese with a BMI >40% [2].

By 2030 it is estimated that 51% of the US population will be obese [3]. Obesity is associated with an increased risk for developing many common chronic medical conditions. This significant and increasing prevalence of obesity poses public

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health as well as economic concerns. According to data from the 2012 National Ambulatory Medical Survey, there were 11 million visits by adults age >20 years old to a physician's office where obesity was listed as a primary diagnosis; this number was up to 12.7 million by 2014, and additional chronic medical condition was associated with 73% of these visits [4, 5].

However there has not been an equivalent increase in the proportion of health care visits by adults with obesity that include counseling on weight loss, nutrition, or physical activity or prescription of weight loss drugs [5]. Primary care physicians are faced with the challenge of screening for and treating obesity and its related complications. The USPSTF recommends screening all adults for obesity and treating those with a BMI of >30 kg/m^2 [6]. The primary care provider remains integral in getting patients engaged in the conversation about weight loss. Primary care providers cite limited time, inadequate knowledge of obesity treatment, and lack of reimbursement as reasons obesity is not addressed [7]. New evidence suggests that under medicalization of this disease may also be a contributing barrier to appropriate obesity care [5].

This text hopes to aid in bridging the knowledge deficit and to add to the expanding body of knowledge on obesity as a medical condition in an effort to enhance patient access to meaningful and successful treatment options for obesity. We provide a review of current and updated best practices for medical evaluation and management of patients with obesity. Approaches to the conversation about weight management and algorithms for treatment will be highlighted.

Key History and Physical Exam

History

Starting the conversation about weight loss is important. Patients considered even a brief conversation with their pri-

mary care provider about how weight loss may improve their health to be motivating, helpful, and appropriate [8]. As with most health issues, the conversation should be broached sensitively. It is recommended that the physician asks the patients' permission to engage in a conversation about their weight and share their concerns regarding the impact on the patient's health [9]. If patients are agreeable, utilize a strategy that focuses on information sharing rather than blaming patients for their weight. Recognize obesity as a medical condition by using language that is agreeable, inoffensive, and clear [10]. The terms fat, obese, and morbidly obese are most associated with stigmatization and blaming, while the terms excess weight, high body mass index, or unhealthy weight are more acceptable and motivating [11]. In addition to further medicalize the condition, it's been recommended that physicians use phrases such as "patients with obesity" rather than "obese patients" [9].

Taking an obesity-focused history includes assessment of historical events surrounding weight gain or loss, paying close attention to the patient's own perception of weight. Major life events that may contribute to weight gain include changes in marital status or employment status, quitting tobacco, pregnancy, and menopause. These events can be plotted on a weight graph to aid in presenting a visual depiction of the trends [10]. The review of medical history should be thorough and include any history of childhood or adolescent obesity.

Assess for any symptoms or signs suggestive of secondary causes of weight gain. For example, a body habitus suggestive of a specific hormone imbalance or genetic anomaly might prompt further testing. A careful review of all medications including all over-the-counter medications should be completed in order to identify and modify any drugs or substances known to promote weight gain. Common weight-inducing prescription medications include beta-blockers, oral corticosteroids, anti-epileptics, sulfonylureas, insulin, atypical antipsychotics, some SSRIs, and hormonal treatments such as progesterone.

Assessment of psychological health including a thorough psychiatric history is essential. Assess for mood or anxiety disorders, eating disorders, post-traumatic stress disorder, psychotic disorders, and substance abuse disorders. Any positive findings should trigger a mental health referral for further assessment prior to initiating any weight management treatment [10].

Assessment of readiness to engage in a weight management regimen should be evaluated. Readiness is primarily determined by the patients' level of motivation and the feasibility of implementing and adhering to a weight-loss plan. Identifying and addressing patient-specific barriers are critical in order for patients to achieve their weight-loss goals. Clarify the patient's expectations and goals and reconcile them with the physician's medical recommendations. It is possible that it may not be the optimal time for the patient to undertake a weight-loss plan. The patient may still be in the pre-contemplative or contemplative stages of behavior change, and physician counseling may serve to catapult them to a stage of readiness to engage in weight-loss activities. Physicians' use of the 5A approach (Assess, Advise, Agree, Assist, Arrange) has been found to lead to improved weight-loss outcomes [12].

Physical Examination and Diagnostics

It has been deemed necessary in more recently developed guidelines to improve upon the diagnosis of obesity by requiring not only BMI calculations but also a system of indicating the degree to which excess adiposity negative affects a patient's health [13]. The focus should be on further assessment for objective findings to quantify and qualify obesity, to determine if any comorbid conditions or secondary contributors to obesity exist, and to direct specific screening or diagnostic testing for obesity related health conditions.

Patients who are obese may experience a great amount of trepidation when seeking medical care as many offices do not

have the appropriate instruments readily available for an accurate and comfortable examination [14]. Always use suitable instruments for a patient's body habitus especially when measuring weight and blood pressure. Often examination gowns/drapes and tables may be too small. These factors may limit the comfort of the patient and also the usefulness and even safety of proceeding with the exam.

Calculate BMI based on an accurate height and weight. Measurement of waist circumference provides additional information regarding predisposition to metabolic disease among individuals with BMI <35 kg/m^2 [10, 13]. Percentage of body fat may be more useful in patients at the extremes in muscle mass and may be a more accurate measure of body composition. Assess blood pressure using an appropriately sized cuff. Examine the skin for signs suggestive of glucose intolerance such as acanthosis nigricans. Conduct a thorough cardiorespiratory, abdominal, and musculoskeletal exam and observe for signs of obesity-related complications (Table 10.1).

The measurement of neck circumference may be useful as part of calculating the STOP-BANG score as a screening tool for sleep apnea [15]. Please see Chap. 15 for more information.

Diagnostic and screening laboratory values such as lipid panel, hemoglobin A1c, thyroid-stimulating hormone level, liver function tests, and an EKG should be completed in addition to any other appropriate evaluations for associated conditions (listed below) based on history and exam findings [10, 13].

Table 10.1 Weight classifications based on BMI

Weight	Body mass index (BMI) (kg/m^2)
Normal	18.5–24.9
Overweight	25.0–29.9
Class 1 obesity	30.0–34.9
Class 2 obesity	35.0–39.9
Class 3 obesity	≥40

*prediabetes *metabolic syndrome *type 2 diabetes *dyslipidemia *hypertension *cardiovascular disease *nonalcoholic fatty liver disease *polycystic ovarian syndrome *female infertility *depression *male hypogonadism *obstructive sleep apnea *asthma *osteoarthritis *urinary stress incontinence *gastroesophageal reflux disease

Who Should Lose Weight?

Results of diagnostic and laboratory testing can be one of the key factors in determining which patients need to lose weight. Weight loss is recommended for individuals with a BMI ≥30 kg/m^2 or BMI 25–29.5 kg/m^2 with adiposity-related complications (see Fig. 10.1). The Edmonton obesity staging system may offer clinical guidance in assessing obesity-related risk and prioritizing treatment (see Table 10.2) [16, 17].

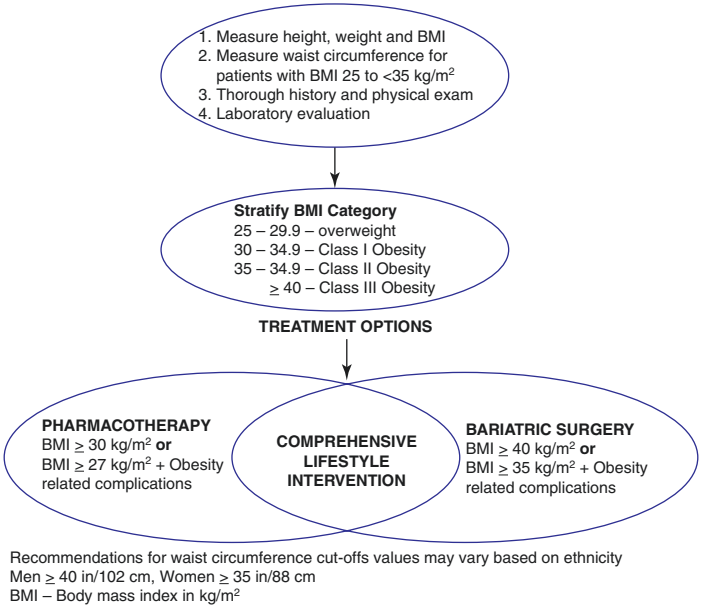

Figure 10.1 Evaluation of a patient with increased weight

Table 10.2 Edmonton staging system [16]

STAGE	0	1	2	3	4
Clinical Complications	*None*	*Mild*	*Moderate*	*Significant*	*Severe or End-Stage*

Treatment

Management of Obesity

Obesity is a complex chronic disease that results from the interaction of genetic, environmental, and behavioral determinants. Adipose tissue becomes a dysfunctional endocrine organ leading to systemic metabolic disease [13]. Therefore, the cornerstone of management of obesity lies on the importance of weight loss which has shown to reduce morbidity (e.g., reduction in the rate of progression to type 2 diabetes, decrease in blood pressure, and plasma lipid levels) and mortality.

Most guidelines have incorporated a "complications centric approach" for management of obesity rather than a preset decline in body weight. The therapeutic endpoint is improvement of obesity-related complications leading to improved patient health and quality of life [18, 19].

Initial treatment includes lifestyle therapy which is the cornerstone of all weight-loss interventions (see Fig. 10.1). An evidence-based *comprehensive lifestyle therapy* for treatment of obesity includes three components provided by a trained interventionist (e.g., exercise specialists, registered dieticians, psychologists, health counselors). The evidence supporting the efficacy of lifestyle intervention or behavioral modification is supported by data from two large randomized clinical trials which have shown that even modest weight loss of 5–10% has a significant impact on the metabolic disturbances associated with obesity [20, 21]. The three main components are as follows:

- Reduced calorie diet
- Physical activity
- Behavior modification to facilitate adherence to diet and activity

Diet

To achieve weight loss, an energy deficit is required; therefore current guidelines recommend reducing total energy (caloric) intake (500–750 kcal daily deficit), and this should be the main component of any weight-loss intervention [13]. The meal plan should be individualized based on personal and cultural preferences. Various types of diets such as Mediterranean, DASH, low-carb, low-fat, volumetric, high-moderate-protein, vegetarian, macronutrient-targeted, and the AHA-style Step 1 diet have been studied. Several randomized clinical trials have shown similar weight loss on diets with different macronutrient composition [22–25]. Diet effectiveness is more related to adherence to the diet than the diet composition. A very-low-calorie diet (≤800 kcal) is an option in select patients using meal replacement options and requires medical supervision [13]. There is evidence that individuals who consumed more calories in the morning than in the evening lost more weight [26, 27], while food intake at night is linked to obesity independent of energy intake [28].

Due to the limited weight loss from continuous energy restriction (CER), there have been recent interest in newer weight loss strategies that involve restricting energy intake to certain periods of the day or prolonging the fasting interval between meals. These strategies include intermittent fasting (IMF; >60% energy restriction on 2–3 days per week or on alternate days) and time-restricted feeding (TRF; limiting the daily period of food intake to 8–10 h or less on most days of the week). Current evidence suggests that these newer strategies produce comparable weight loss to CER [29].

With dietary intervention in overweight and obese adults, average weight loss is maximal in 6 months, with smaller losses maintained for up to 2 years during tapering of treatment and follow-up [30].

Physical Activity

The typical prescription included in a lifestyle intervention is as follows [13]:

Aerobic physical activity (such as brisk walking) progressing to 150 min/week performed on 3–5 separate days per week.

Resistance exercise single-set repetitions involving major muscle groups, two to three times per week to maximize fat loss while preserving lean mass.

Reduction of sedentary behavior to increase overall energy expenditure.

Higher levels of physical activity, approximately 200–300 min/week, are recommended to maintain lost weight or minimize weight gain in the long term (>1 year). A combination of aerobic and resistance is better than either alone.

Behavior therapy A structured behavior change program should be offered, utilizing a multidisciplinary team that includes any number of the following:

Self-monitoring of food intake, exercise and goal setting, education (face-to-face individual or group sessions or remotely, i.e., telephone), problem-solving strategies, stimulus control, behavior contracting, stress reduction, cognitive restructuring, motivational interviewing, and psychological evaluation and counseling with treatment if needed. These same behaviors are recommended for weight-loss *maintenance*, with the addition of frequent monitoring of body weight (weekly or more often). Behaviors that support lifestyle changes help people achieve and sustain weight loss.

Pharmacotherapy

Drugs for overweight and obesity should be used only as an adjunct to lifestyle therapy and not alone.

Pharmacotherapy can be *considered*:

- In individuals with a BMI $\geq$30 kg/m^2, without complications in whom lifestyle therapy fails to achieve weight-loss goals.
- In individuals with a BMI $\geq$27 kg/m^2, with one or more complications in whom lifestyle therapy fails to achieve weight-loss goals.

Pharmacotherapy is *initiated*:

- When lifestyle therapy alone fails and the patient progressively gains weight or has no clinical improvement in weight-related complications.

The addition of pharmacotherapy produces greater weight loss and weight-loss maintenance compared to lifestyle therapy alone and leads to a longer duration of maintained weight loss [31]. In selecting the optimal weight-loss medication for each patient, clinicians should consider differences in efficacy, side effects, cautions, and the presence of weight-related complications and medical history. Pharmacotherapy should be offered when potential benefits outweigh the risks of chronic treatment of the disease. Medications that contribute to weight gain should be discontinued if possible. Weight-loss medications should be avoided in women who are pregnant or planning pregnancy. It is recommended that weight-loss medications be discontinued after 12 weeks if weight loss does not exceed 5% of body weight.

Weight-loss medications approved by the Food and Drug Administration (FDA) for the short-term use (3 month) is phentermine, while for the long-term use in the treatment of obesity are orlistat (Xenical Alli), phentermine/topiramate extended-release combination (Qsymia), naltrexone ER/bupropion ER (Contrave), liraglutide 3 mg (Saxenda), and semaglutide (Wegovy) which is the most recent addition in June 2021. Previously approved lorcaserin (Belviq) was voluntarily withdrawn from the market in February 2020 [32].

See Tables 10.3 for specific information about each drug.

Weight-Loss Surgery and Procedures

In obese adults, bariatric surgery is more effective than conventional medical treatment, lifestyle intervention, or medically supervised weight loss. The Swedish Obese Subjects study followed 2000 patients up to 20 years after surgery which included banded gastroplasty, gastric banding, and Roux-en-Y gastric bypass done by open techniques. There

Table 10.3 Weight-loss medications: an overview

Medication (dosing)	Mechanism of action	% Total body weight loss	Side effects	Contraindications
Short-term weight loss				
Phentermine [40] (schedule IV-controlled substance) 15–37.5 mg daily	Adrenergic agonist induces weight loss by release of norepinephrine leading to decrease in appetite	(7.5 mg) 5.5% (15 mg) 6.1%	Dry mouth, difficulty in sleeping, irritability	Pregnancy, breast feeding, cardiovascular disease, uncontrolled hypertension, glaucoma, hyperthyroidism
Long-term weight loss				
Orlistat (*Xenical*) 120 mg PO TID before meals Over-the-counter 60 mg PO TID before meals	Orlistat induces weight loss by blocking dietary absorption of fat	1 year—4.0% 4 year—2.6%	Steatorrhea, fecal urgency, incontinence, flatulence, oily spotting, frequent bowel movements, abdominal pain, headache	Pregnancy and breastfeeding, chronic malabsorption syndrome, cholestasis, oxalate nephrolithiasis

(continued)

Table 10.3 (continued)

Medication (dosing)	Mechanism of action	% Total body weight loss	Side effects	Contraindications
Phentermine/topiramate ER (*Qsymia*) Starting dose: 3.75/23 mg PO QD for 2 weeks Recommended dose:7.5/46 mg PO QD Escalation dose: 11.25/69 mg PO QD Maximum dose: 15/92 mg PO QD	Topiramate is an anticonvulsant, which has been shown to increase weight loss in obese patients Phentermine is a norepinephrine-releasing agent	1 year—6.6–7.5%	Headache, paresthesia, insomnia Decreased bicarbonate, xerostomia, anxiety, depression, constipation, dizziness, nausea	Pregnancy and breastfeeding (topiramate teratogenicity) Concomitant monoamine oxidase inhibitor (MAOI) use within 14 days, hyperthyroidism, glaucoma, cardiovascular disease or history
Naltrexone ER/bupropion ER (*Contrave*) Dose titration: Week 1: 1 tablet (8/90 mg) PO QAM Week 2: 1 tablet (8/90 mg) PO BID Week 3: 2 tabs (total 16/180 mg) QAM and 1 table (8/90 mg) Q HS Week 4: 2 tabs (total 16/180 mg) PO QHS	*Bupropion* is a mild reuptake inhibitor of dopamine and norepinephrine *Naltrexone*, an opioid antagonist	1 year—4.2–5.2%	Nausea, headache, insomnia, vomiting, constipation, diarrhea, dizziness, anxiety, xerostomia	Pregnancy and breastfeeding, uncontrolled hypertension, seizure disorder, concomitant MAOI (within 14 days), long-term opioid or opiate agonists use or acute opiate withdrawal, anorexia nervosa

Liraglutide 3 mg—(Saxenda) Titrate dose weekly by 0.6 mg as tolerated up to a maximum dose of 3 mg subcutaneously daily	Long-acting GLP-1 (glucagon-like peptide) analog	1 year—5.6%	Nausea, vomiting, diarrhea, constipation, headache, dyspepsia, increased heart rate	Pregnancy and breastfeeding, personal or family history of medullary thyroid cancer, pancreatitis, acute gall bladder disease, gastroparesis
Semaglutide 2.4 mg (Wegovy) [41–44] 2.4 mg per week	Long-acting GLP-1 (glucagon-like peptide) analog	Lost 12.4%—68 weeks	Increased risk of diabetic retinopathy nausea, vomiting, diarrhea, constipation, headache, dyspepsia, increased heart rate	Pregnancy and breastfeeding, personal or family history of medullary thyroid cancer, pancreatitis, acute gall bladder disease, gastroparesis

was a 24% reduction in overall mortality, obesity-related morbidity (e.g., decreased incident rates of diabetes, hypertension, dyslipidemia), and improvements in quality of life in the bariatric surgery group compared with the conventionally treated group [33]. Recent studies in US populations also support the enduring nature of these outcomes long term [34]. However, despite the growing prevalence of obesity and demonstrated efficacy and safety of bariatric surgery, only ~0.5% of eligible patients receive this treatment [2]. While the internist does not perform surgery, primary care physicians play an important role in terms of identifying patients who may benefit from surgery, advising them to consider this option and referring to a skilled bariatric surgery team for evaluation if deemed appropriate [35].

Surgical intervention is indicated and consistently covered by insurance carriers for patients with the following:

- BMI of ≥40 kg/m^2 who have failed comprehensive lifestyle therapy and pharmacological means
- BMI of ≥35 kg/m^2 with one or more severe obesity-related complications (who have not met weight-loss goals) if the anticipated benefits outweigh the risks, side effects, and cost of the surgical procedure

Consensus guidelines now also recognize the following additional indications for surgery though not yet widely covered by medical insurance carriers [36]:

- Patients with diabetes or metabolic syndrome with a BMI of 30–34.9 kg/m^2 with inadequate glycemic control despite optimal lifestyle and medical therapy [2, 13]
- Patients with a BMI >27 kg/m^2 in persons of Asian descent with comorbid diabetes mellitus
- Patients at any weight, to achieve optimal health and quality of life when the amount of weight loss needed to prevent or treat clinically significant obesity-related complications cannot be obtained using nonsurgical therapy

The procedures that are commonly used include the following:

- Laparoscopic adjustable gastric banding
- Laparoscopic sleeve gastrectomy
- Roux-en-Y gastric bypass

Laparoscopic sleeve gastrectomy comprises 70% of currently performed procedures, followed by laparoscopic gastric bypass (25%), adjustable gastric banding (3%), and duodenal switch (2%) [36]. *See Tables 10.4 for more information about common surgical options.*

Newer procedures that have been FDA approved include aspiration therapy and space-occupying gastric devices. FDA trials of gastric emptying devices are underway [36]. These novel procedures are considered as possibly suitable for patients being bridged to surgery or for those who have failed non-invasive interventions and are too high risk for surgical intervention [37]. Non-surgical procedures may be considered in patients who may benefit from short-term interventions with high chance of maintaining lifestyle changes for sustained weight loss [36].

Long-Term Follow-Up After Uncomplicated Bariatric Surgery

Patients who have undergone bariatric surgery need lifelong follow-up visits. Follow-up with a multidisciplinary team consisting of the bariatric surgeon, medical obesity specialists, endoscopists, nurses, registered dietician, psychologists, exercise physiologists, and support groups is important to optimize results post-surgery. Obesity-related complications should be reviewed and medications adjusted as needed during follow-up. Metabolic deficiencies commonly seen with RYGB (e.g., serum calcium, iron, B12, vitamin D, folate, and thiamine) should be assessed at 3 and 6 months and then annually after surgery [36]. It is now estimated that 25–35%

Table 10.4 Surgical techniques and outcomes [26, 27]

	Weight loss	Long-term complications >30 days post-surgery	Comorbidity remission outcome (estimates in % from RCT)
Gastric bypass	60–85%	Dumping syndrome Marginal or gastrojejunal ulcers Cholelithiasis Nephrolithiasis Depression	Mortality ≤30 days—0.08% (0.01–0.30), n = 934 Mortality >30 days—0.39% (0.01–0.86), n = 954 Complication rates—21(12–33), n = 649 Diabetes remission rates—95.15 (88.38–98.80), n = 152 Hypertension remission rates—80.98 (68.2–91.5), n = 183 Dyslipidemia remission rates—80.16 (61.6–94.1), n = 147
Adjustable gastric band	45–55%	Cholelithiasis	Mortality ≤30 days—0.11 (0.01–0.50), n = 743 Mortality >30 days—0.14 (0.00–0.55), n = 613 Complication rates—13 (5.2–26), n = 855 Diabetes remission rates—73.8 (36.0–96.1), n = 35 Hypertension remission rates—53.55 (12.5–89.6), n = 27 Dyslipidemia remission rates—39.9 (4.69–87.0), n = 132
Sleeve gastrectomy	55–80%	Stenosis leading to gastric outlet obstruction Cholelithiasis	Mortality ≤30 days—0.50 (0.01–3.88), n = 40 Mortality >30 days—6.00 (0.00–100.00), n = 40 Complication rates—13 (0.7–44), n = 137 [a]Diabetes remission rate—NA [a]Hypertension remission rate—NA [a]Dyslipidemia remission rate—NA

[a] Not enough long-term data was available for sleeve gastrectomy remission rates in the analysis

of patients experience weight regain after bariatric surgery, and therefore it is important to monitor patients closely and consistently to help in preventing and managing weight regain [38]. There is also a growing body of evidence supporting an increased risk of alcohol use disorder (AUD) after bariatric surgery procedures, so this should be discussed with patients prior to surgery. The incidence seems to be highest 2 years after surgery, so physicians should continue to vigilantly screen and counsel patients regarding the increased risk at their follow-up visits [36, 39].

Clinical Pearls

- Undesirable terms such as "heaviness," "fat," "large size," "excess fat," and "fatness" and even the term "obese" should be avoided when addressing issues regarding weight.
- Lifestyle modification is the foundation of all treatment algorithms.
- Weight-loss medications should not be prescribed to women who are pregnant or breastfeeding. Women of reproductive age should be using a reliable contraceptive method.
- Obesity is a chronic disease and requires ongoing treatment. Patients will have varying motivation and adherence and will need ongoing encouragement.
- Patients and sometimes physicians have unrealistic weight-loss goals, and it is important to establish realistic and achievable goals. A 5–10% weight reduction is clinically significant and may take 6 months or more to accomplish.

Don't Miss This!

- Even a brief conversation with their primary care provider can make a difference in patient's perceptions of excess weight as a medical issue. Remember to ask patients permission before initiating conversations about their weight. Be sensitive and nonjudgmental in your approach to all conversations regarding weight management.

- Medications are FDA approved for the chronic long-term treatment of obesity and can be prescribed in the appropriate patient.
- Surgery is effective and safe in appropriately selected patients (Tables 10.3 and 10.4).

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Part III
Respiratory

Chapter 11
Cough

Israa Soghier and Kiyoshi Kinjo

Brief Introduction

Cough is one of the most common presentations to both primary and secondary care providers. Globally, the prevalence of chronic cough is estimated at 9.6% of adults [1]. In most cases, the cause of cough can be identified with history taking, physical examination, and simple diagnostic tests. Sometimes, chronic cough can be challenging to manage and will require referral to a specialist.

Decision-Making/Differential Diagnosis

The first step to determine the etiology of cough is to estimate the duration of the symptom at the time of presentation to the provider. Acute cough lasts for less than 3 weeks while

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subacute cough has a duration of 3–8 weeks. Cough lasting for longer is considered chronic cough [2].

Acute Cough

Acute cough is most commonly caused by viral upper respiratory infections. Other causes include pneumonia, bacterial tracheobronchitis, pertussis, acute exacerbations of chronic conditions like asthma, chronic obstructive pulmonary disease (COPD) or bronchiectasis, congestive heart failure (CHF), and pulmonary embolism (PE). Tuberculosis should be considered in patients from endemic areas and in high-risk populations regardless of the duration of the cough. Acute cough can also be an early presentation of subacute or chronic cough. Other etiologies include foreign body inhalation, inhalational injury, pneumothorax, and some types of interstitial lung disease such as acute interstitial pneumonia and hypersensitivity pneumonitis.

Subacute Cough

Subacute cough is most often postinfectious. Bordetella pertussis may play a role in unvaccinated patients with exposure to young children. Other causes include exacerbations of asthma, COPD, or upper airway cough syndrome and overlap with chronic cough.

Chronic Cough

Chronic cough is evaluated with a stepwise approach. After excluding life-threatening causes, e.g., cancer and tuberculosis, diagnostic work-up should focus on asthma, COPD, gastroesophageal reflux (GERD), non-asthmatic eosinophilic bronchitis, and upper airway cough syndrome. More than one condition was found to be contributing to the persistence of

chronic cough in up to 62% of patients [2]. Uncommon causes of chronic cough include sleep apnea, chronic aspiration, recurrent tonsillitis, external ear canal irritation (e.g., earwax impaction), and psychogenic causes. Approximately 5–10% of patients will have unexplained chronic cough that remains undiagnosed after investigation and trial of therapy [3]. Referral to specialists (pulmonary, otolaryngology, or gastroenterology) is necessary.

Evaluation/Investigation

History taking should focus on the duration of the cough and presence of associated symptoms like upper airway symptoms, wheezing, dyspnea, sputum production, and heartburn. One study suggested that the characteristics and timing of the cough were not usually helpful in differentiating the common causes [4]. Significant sputum production points to an underlying pulmonary disease, e.g., bronchiectasis. The American College of Chest Physicians recommends actively searching for red flags (Table 11.1; Fig. 11.1) [5]. Symptoms of whooping cough (paroxysmal cough, posttussive vomiting, inspiratory whooping, and absence of fever) should be elicited in patients with cough lasting 14 days or more [6].

Many patients report cough starting after an upper respiratory tract infection. Searching for triggers/aggravating factors including exposures, both at home and at work, travel, tobacco use, illicit drugs, and vaping may help identify the etiology. Some prescription drugs are frequently associated with cough, e.g., angiotensin converting enzyme inhibitors. Case reports suggest sitagliptin may also cause or exacerbate cough, particularly in those with a history of allergic rhinitis [7]. A history of past respiratory or cardiac disease should be elicited. A family history of cough can be seen in atopic patients and in those with an anatomic or neurological abnormality [8, 9]. The history should also reveal the presence of a foreign body or inhalation injury.

Table 11.1 Clinical Symptoms and risk factors for serious pulmonary disease

Red flags
Smoker >45 years with a new cough, change in cough, or voice disturbance
Adults at increased risk of lung cancer (aged 50–80 years who have a 20 pack-year smoking history and currently smoke or who have quit within the past 15 years)
Hemoptysis
Dyspnea
Hoarseness
Systemic symptoms: Fever, Weight loss
Lower extremity edema
Dysphagia
Vomiting
Recurrent pneumonia
Abnormal respiratory exam
Abnormal chest imaging

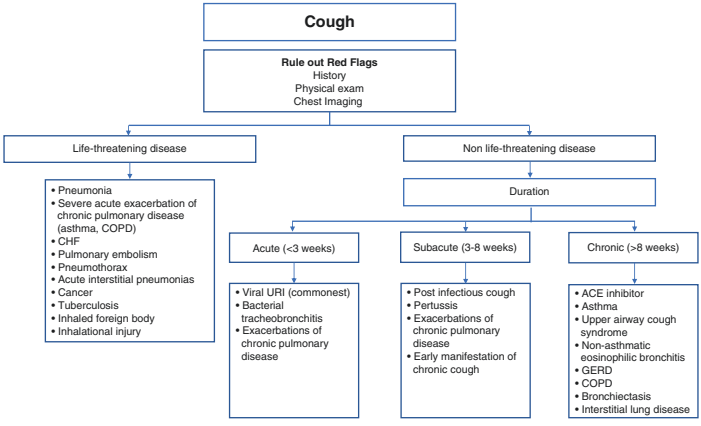

Figure 11.1 Management of cough

Disease-Specific Features

Acute Cough

Acute cough is relatively easy to evaluate. When a patient presents with cough accompanied by fever, rhinorrhea, malaise, and myalgia/arthralgia with history of a sick contact and they look relatively healthy, the likely diagnosis is upper respiratory infection. Current guidelines do not recommend routine investigations, e.g., chest X-ray, spirometry, sputum cultures, or viral respiratory panels as there is little evidence for benefit [10].

Influenza has similar symptoms but is usually more severe and can only be differentiated from viruses causing common cold by specific testing. It can cause serious complications such as pneumonia, acute respiratory distress syndrome, multiorgan failure, and death. Certain patients are more susceptible to poor outcomes, specifically elderly patients (>65 years) and those with chronic diseases like diabetes, heart failure, chronic pulmonary diseases, renal failure, cancer, and immunosuppressive conditions [11].

Pneumonia is usually not accompanied by rhinorrhea or other upper respiratory symptoms. Purulent sputum is commonly seen in pneumonia but purulence is not specific to pneumonia (sinusitis and bronchitis can be also associated with purulent sputum). "Atypical pneumonia" presents often with dry cough. Bronchial breathing or crackles can be heard when auscultating the chest.

The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) recommend using a prediction score, either the CURB-65 score [12] or the Pneumonia Severity Index (PSI) [13], to determine whether the patient can be treated as an outpatient or requires hospitalization [14, 15]. Implementing the PSI results in fewer admissions without an increase in adverse events [16]. Other factors should also be taken into consideration, e.g., the ability to reliably take oral medications, the patient's functional status, other comorbidities, and their social situation. Beyond

chest imaging, obtaining routine diagnostic tests to identify an etiologic diagnosis, e.g., blood and sputum culture is not currently recommended for patients with community-acquired pneumonia (CAP) treated at home due to their low yield and failure to demonstrate an improvement in outcome [14, 17]. Blood cultures also generate false positives from skin contaminants and increase unnecessary antibiotic use [18]. Testing for influenza with a nucleic acid amplification test is recommended in periods of high influenza activity in the community because of the benefit of added antiviral therapy to antibiotics and infection prevention. In contrast, testing for pneumococcal Ag and legionella is not recommended except in severe CAP or if indicated due to outbreaks or travel.

Acute exacerbation of asthma, COPD, or CHF in patients with a history of known illness can be easily diagnosed by history and physical exam. Chest imaging showing pulmonary edema can confirm CHF. All three can present with cough accompanied by dyspnea, orthopnea, and wheeze. (Table 11.2). Patients with asthma tend to get worse very early in the morning.

Clinical presentation of PE is variable but patients rarely present only with cough. They usually complain of sudden onset dyspnea, pleuritic chest pain, hemoptysis, or syncope.

Table 11.2 Differentiating symptoms between asthma, COPD, and CHF exacerbation

	Asthma	**COPD**	**CHF**
Cough	Dry/scant sputum	Increased sputum production or purulent sputum	Frothy pink sputum
Wheezing	+	+	+/–
Orthopnea	+	+	+
Night symptom	Late night to early morning		Early night
Leg edema	–	–	Often
Weight gain	–	–	+

Symptoms of deep vein thrombosis (leg swelling and pain) may be present. Pulmonary embolism should always be included in the differential diagnosis in patients with risk factors but these patients tend to be sicker, and, therefore, more often visit emergency rooms rather than the outpatient office.

Subacute Cough

The severity of postinfectious cough is quite variable and can be disabling in some cases (e.g., sleep disturbance, stress incontinence, and posttussive vomiting). In most cases, the patient may recall a preceding episode of fever and upper respiratory symptoms. Some report persistent nasal symptoms indicating postnasal drip as a mechanism of cough. In adults, paroxysmal whooping cough spells and posttussive vomiting have a low sensitivity (32.5% [95% CI, 24.5–41.6] and 29.8% [95% CI, 18.0–45.2]) but high specificity (77.7% [95% CI, 73.1–81.7] and 79.5% [95% CI, 69.4–86.9]) in the clinical diagnosis of pertussis. Fever and absence of cough paroxysms suggest pertussis is unlikely the cause [6]. Pertussis can be diagnosed by nasopharyngeal culture, polymerase chain reaction (PCR), and serology [19]. It is important to determine the vaccination status and whether there is a possible exposure to young children to identify pertussis, where early treatment may be potentially helpful.

Chronic Cough

Chronic cough is more prevalent in middle-aged females. Women have more frequent cough than men and have heightened cough reflex sensitivity [20]. The first step is to rule out the serious and common causes by history, physical examination, chest X-ray, and spirometry. The presence of weight loss, fever, night sweats, chest pain, and hemoptysis suggests life-threatening diseases, e.g., lung cancer and tuberculosis [8]. Further work-up including sputum testing and chest computed tomography (CT) should be considered.

Drug-induced cough, especially due to angiotensin-converting enzyme (ACE) inhibitors, is common (about 16%) [21] and tends to be dry. It starts within 1–2 weeks after the initiation of ACE inhibitors but can be delayed up to 6 months. The cough subsides when the drug is discontinued usually within 4 weeks [22].

Bronchiectasis, COPD, and various parenchymal lung diseases can be identified by chest imaging and spirometry. Patients often have exertional dyspnea which can go unnoticed because they attribute that to their smoking. It is helpful to ask the family about the patient's exercise capacity. Localized or unilateral wheezing may suggest an endobronchial lesion (cancer or foreign body). Chest CT should be ordered. The patient should be referred to a pulmonologist for bronchoscopy.

Once the serious causes are excluded, the four most frequent etiologies of chronic cough are asthma, non-asthmatic eosinophilic bronchitis, GERD, and upper airway cough syndrome [8, 23, 24] (Fig. 11.2). These conditions may present with cough and typical symptoms but many patients have only cough. Thus, empirical (diagnostic) treatment is tried in many cases before an extensive work-up is undertaken.

Asthma usually presents with episodic dyspnea and wheezing in addition to cough. Occasionally, cough can be the only symptom, an entity known as "cough variant asthma." A personal or family history of atopy or recent initiation of a beta blocker can be helpful. Spirometry showing reversible airway obstruction is often seen in asthma. If the pulmonary function test is normal, a methacholine challenge test, sputum eosinophils, or elevated exhaled nitric oxide may assist in diagnosis. Non-asthmatic eosinophilic bronchitis is difficult to distinguish from asthma clinically. Sputum eosinophilia without bronchial hyperresponsiveness is diagnostic.

Patients with upper airway cough syndrome have nasal discharge, a sense of postnasal drip or the urge to clear their throat leading to cough. Cobblestone appearance and secretions may be seen in the nasopharynx. Treatment with nasal steroids or antihistamines is recommended, especially for patients with a history of allergic rhinitis or chronic sinusitis.

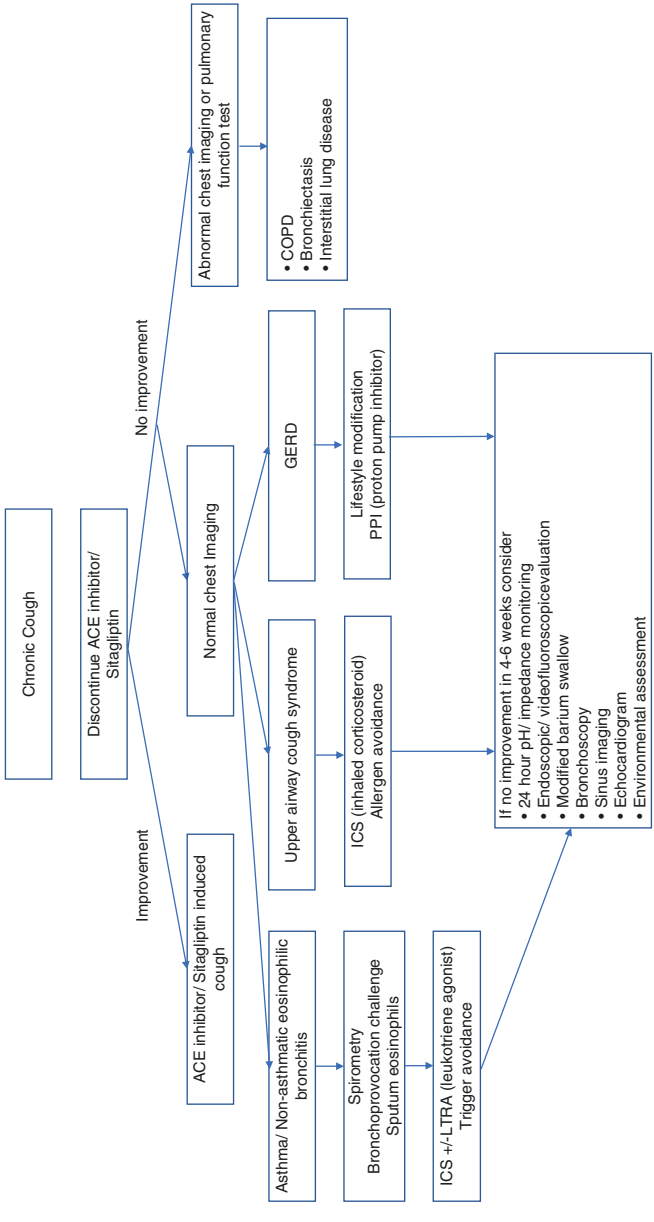

FIGURE 11.2 Management of chronic cough

Treatment

Once the etiology is found, a specific treatment can be instituted. This should be followed by an evaluation in 4–6 weeks. Any unresolved cough should be referred to a specialist or preferably a cough clinic if available.

Acute cough is usually self-limited and requires only reassurance [10]. Patients have reported relief from the use of over-the-counter medications, e.g., dextromethorphan, menthol, and first-generation antihistamines. There is no role for antibiotics except in the treatment of cough due to bacterial pneumonia, pertussis, and severe COPD exacerbations.

In pertussis, macrolides for 5–7 days decrease the spread of the disease. The CDC recommends early antibiotic initiation within the first 2 weeks to decrease the duration of symptoms [25, 26] but a Cochrane review found it does not alter the clinical course of the disease [27]. When suspected, treatment should be started without waiting for laboratory confirmation. There is insufficient evidence to recommend other interventions, e.g., corticosteroids, antihistamines, beta2-adrenergic agonists, leukotriene receptor antagonists, or pertussis-specific immunoglobulin in the symptomatic management of pertussis-related cough [28].

For influenza-related cough, antivirals should be initiated preferably within 48 h in patients who are very ill or at high risk for serious influenza-associated complications. Antiviral drugs have proven to reduce the duration of illness, ameliorate symptoms and prevent hospitalizations and death [29, 30]. The mainstays of treatment for acute exacerbations of COPD and asthma are steroids and bronchodilators.

Patients with cough caused by asthma and non-asthmatic eosinophilic bronchitis should be given inhaled corticosteroids as first-line treatment [31, 32]. If the response is inadequate, clinicians should consider increasing the dose of the inhaled steroid and trial of a leukotriene inhibitor [33, 34]. Some patients with asthma may require oral glucocorticoids for 1–2 weeks [3]. Alternative causes of cough should also be

sought. It is important to try to identify possible triggers/allergens and encourage avoidance.

When GERD is suspected, lifestyle modification measures are recommended. These include diet modification, elevation of the head of the bed, avoidance of food 3 h before bedtime, and weight loss in obese patients [35]. For patients who have symptoms of reflux (heartburn and regurgitation), pharmacologic therapy can be initiated. Proton pump inhibitors should not be prescribed alone without lifestyle modification in cough reflux syndrome if there are no reflux symptoms because they are unlikely to be effective [36]. Improvement in symptoms may take up to 3 months. If there is no response after therapeutic trial, referral for pH monitoring study and esophageal manometry should be considered if there is a strong clinical suspicion warranting diagnostic confirmation, e.g., those undergoing surgery for reflux [37].

Patients suffering from cough due to stable COPD should be treated according to the GOLD guidelines [38]. Smoking cessation and avoidance of environmental triggers help alleviate the severity of cough. There is insufficient evidence to recommend other treatments, e.g., antibiotics, cough suppressants, or mucolytics to specifically target cough [39].

In addition, avoidance of occupational and other toxic substances is a key aspect in controlling cough when an external inhalational trigger is suspected. Treatment will depend on the disease manifestation, e.g., prescribing oral corticosteroids for hypersensitivity pneumonitis. Referral to a pulmonologist is usually required for specialist testing.

Unexplained chronic cough is usually managed with the aid of a pulmonologist. These patients may benefit from speech therapy [40] or a trial of gabapentin with reevaluation of the risk-benefit profile [41].

Clinical Pearls

- Cough should be approached based on the duration of the symptom.
- A thorough history and physical exam should give clues to the correct diagnosis in many cases.

- When patients present with chronic cough and no other obvious symptoms, asthma, GERD, and upper airway cough syndrome should be considered.

Do Not Miss This!

- Many serious diseases such as COPD, lung cancer, interstitial pneumonia, and tuberculosis present with cough. These should be excluded by history, physical examination, chest X-ray, and spirometry, before thinking about asthma, GERD, and upper airway cough syndrome.
- Weight loss, fever, night sweats, and hemoptysis suggest a serious disease like tuberculosis or cancer. You should get a chest X-ray/CT and sputum for acid-fast bacilli.
- Unilateral wheezing suggests an endobronchial lesion, e.g., cancer or a foreign body. Get a chest CT and refer to a pulmonologist for bronchoscopy.

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Chapter 12
Shortness of Breath

Kiyoshi Kinjo

Introduction

Dyspnea of acute onset may suggest serious and potentially life-threatening illness. When the vital signs are abnormal and the patient looks acutely ill, the diagnosis and treatment need to be provided expeditiously; in many instances, the best approach would be to transfer the patient to the emergency room [1].

Chronic dyspnea should be approached systematically. Pulmonary and cardiac abnormalities, anemia, and obesity/deconditioning are the most common etiologies [2].

Decision-Making/Differential Diagnosis and Key History and Physical Exam

The onset and duration of dyspnea can be divided into four categories: sudden-onset, acute, episodic, and chronic dyspnea (Fig. 12.1).

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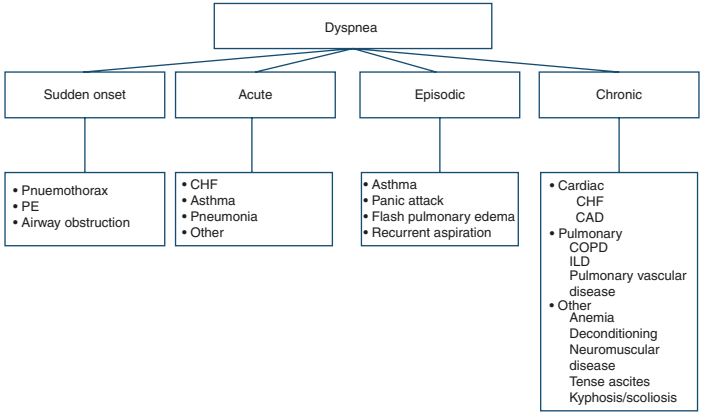

FIGURE 12.1 Differential diagnosis of dyspnea. *PE* pulmonary embolism, *CHF* congestive heart failure, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *ILD* interstitial lung disease

Sudden-Onset Dyspnea

When the patient can tell what he/she was exactly doing at the onset of dyspnea, the likely differential diagnoses are pneumothorax, pulmonary embolism, and acute airway obstruction (foreign body or anaphylaxis).

Spontaneous pneumothorax is often seen in young slender men who smoke. Secondary pneumothorax is mostly seen in patients with known chronic lung diseases such as COPD (chronic obstructive pulmonary disease). Patients can sometimes recall straining during exercise or reaching out an arm when he/she develops sudden dyspnea, often accompanied by pleuritic chest pain.

Pulmonary embolism (PE) can present with sudden-onset dyspnea, pleuritic chest pain, syncope, or hemoptysis. When considering PE, the risk factors should be reviewed, and validated clinical prediction rule (such as Wells score; see Table 12.1) should be used [3]. When the patient with sus-

Table 12.1 Wells prediction rule (simplified score)

Clinical characteristic	Score
Previous PE or DVT (deep vein thrombosis)	1
Heart rate >100 beats/min	1
Surgery or immobilization within the past 4 weeks	1
Clinical signs of DVT	1
Alternative diagnosis less likely than PE	1
Hemoptysis	1
Active cancer	1

Modified from Gibson NS, Sohne M, Kruip MJHA et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism Thrombosis and Haemostasis 2008;99:229–34

Pretest probability

≤1: PE unlikely (low)

>1: PE likely (high)

pected acute PE is hemodynamically unstable, he/she needs to be transferred to the emergency room. In massive PE, thrombolytic therapy might be beneficial.

If the pretest clinical probability is low, one can order D-dimer; if D-dimer is negative (<500 ng/mL), PE can be safely ruled out. When D-dimer is positive, additional imaging is necessary. When the pretest probability is high, the patient needs evaluation in the emergency room (CT pulmonary angiography or VQ scan). If the transfer and imaging studies take time, one should consider starting empirical anticoagulation therapy in the absence of contraindication, pending definitive diagnostic workup.

Diagnosis of acute airway obstruction is usually obvious based on the history of aspiration or signs of anaphylaxis (lip and tongue swelling, urticaria, tachycardia, and hypotension) and stridor.

Acute-Onset Dyspnea

The most common causes in this category are congestive heart failure (new onset or exacerbation), asthma attack, and pneumonia. With history (by paying attention to risk factors and associated symptoms), physical examination, and simple tests including chest X-ray, electrocardiogram, and BNP (brain natriuretic peptide), it is usually easy to reach the correct diagnosis [4].

Congestive heart failure (CHF) is characterized by dyspnea, which is worsened by lying flat (orthopnea), nocturia, weight gain, and bilateral lower extremity edema. Many patients have cardiovascular risk factors: when those risks are absent, acute valvular heart disease (including infective endocarditis (IE)) or acute myocarditis should be considered.

On physical examination, one should look for jugular venous distension, lower extremity edema, bilateral lower lung crackles and heart gallop, laterally displaced PMI (point of maximal impulse), and possibly cardiac murmurs (implying underlying valvular heart disease). Occasionally, wheezing can be heard, and the patient may even respond to a beta-agonist bronchodilator.

Asthma exacerbation typically presents with acute-onset dyspnea, cough (mostly dry), and chest tightness, which is worse late at night or early in the morning, often triggered by upper respiratory infections. In many cases, wheezing can be easily audible, but in a severe asthma attack with impending respiratory failure, wheezing may diminish or become absent. History of allergy (atopic dermatitis, allergic rhinitis, or conjunctivitis) as well as family history of asthma and allergy is helpful.

Pneumonia is not difficult to diagnose when a patient presents with typical symptoms such as fever and cough with purulent sputum, but the presentation can be quite variable [5]. Many elderly may have no fever, but present with appetite loss, impaired mental status, or acute decline from baseline ADLs (activities of daily living) [6]. Atypical pneumonia can present with GI symptoms or headache. Tachycardia or tachypnea may be the only clue to the correct diagnosis.

Other etiologies of acute dyspnea can be identified by history, physical examination, chest X-rays, and electrocardiogram in most cases.

Episodic Dyspnea

When a patient presents with recurrent episodes of dyspnea, the common diagnoses to consider are (1) asthma, (2) panic attack, (3) flash pulmonary edema, and (4) recurrent aspiration.

Panic attack is characterized by episodes of intense fear accompanied by somatic complaints including dyspnea. Although it is important to exclude other medical illnesses, patients with typical features of panic disorders would benefit from early psychiatric evaluation and treatment including cognitive behavioral therapy.

Flash pulmonary edema presents with an acute episode of pulmonary edema, presenting like acute CHF, but can be caused by a noncardiac infirmity such as bilateral renal artery stenosis [7].

Elderly with advanced dementia or patients with underlying neuromuscular disorders may develop intermittent aspiration with desaturation. Rhonchi and wheezing are often detected when the patient becomes dyspneic.

Chronic Dyspnea

Etiology of chronic dyspnea can be divided into three categories: (1) cardiac, (2) pulmonary, and (3) others. One should always consider and thoroughly evaluate each category since more than one cause may coexist, especially in the elderly (e.g., COPD and coronary artery disease). When dyspnea seems out of proportion to the severity of one disease, another overlapping condition may be present.

The most common etiologies are (1) CHF, (2) COPD, (3) interstitial lung disease, (4) asthma, (5) anemia, and (6) obesity/deconditioning (Table 12.2).

Table 12.2 Common causes of chronic dyspnea

Diagnosis	History	Physical exam	Diagnostic test
CHF	History of coronary artery disease, hypertension, valvular disease, orthopnea, edema, weight gain	Jugular venous distension, lower extremity edema, bibasilar crackles, gallop sound, AFib	Electrocardiogram Chest X-ray Echocardiography BNP
COPD	>50 years old with significant smoking history, chronic cough, sputum	Distant lung sounds, barrel chest, wheezes	Chest X-ray PFT
Interstitial lung disease	Chronic dry cough, h/o occupational exposure, rheumatic disease	Bibasilar fine crackles, clubbing	Chest X-ray and chest CT PFT
Asthma	Episodic wheezy dyspnea, triggered by URI, seasonal changes	Wheezes	PFT with bronchodilator response
Anemia	Dyspnea on exertion	Pale conjunctiva	Hemoglobin Workup underlying cause of anemia
Obesity/ deconditioning	Dyspnea on exertion, sedentary lifestyle, obesity	Normal or obese	Exclude other etiologies

Although many interstitial lung diseases are chronic, acute interstitial pneumonia, acute eosinophilic pneumonia, pneumocystis pneumonia, and dermatomyositis-associated lung disease may present acutely or subacutely.

Other less common diagnoses to consider may include lung cancer, pleural effusion, pulmonary hypertension, tense ascites, neuromuscular diseases, and chest wall deformity.

When the diagnosis remains elusive after routine evaluation, pulmonary or cardiology consultation should be considered. In difficult cases, cardiopulmonary exercise testing may be helpful [8].

Treatment

Once the etiology is identified, the specific treatment can be provided.

The stepwise asthma treatment is shown in Table 12.3 [9]. In most cases, symptoms of asthma can be managed with low-dose inhaled corticosteroids (ICS). A recent guideline recommends the use of ICS-formoterol (LABA) as both controller and reliever; even patients with infrequent asthma symptoms are at risk for severe exacerbation. Patients often use only short-acting beta agonist inhaler without ICS. Overuse of beta agonist is a risk factor for fatal asthma. Patients who cannot use the steroid inhaler despite repeated instructions (e.g., cognitive impairment or hand deformity) may use a leukotriene receptor antagonist, although it is less effective. Patients with more frequent, more severe symptoms should be treated with a low-dose steroid and a long-acting beta-agonist (ICS-LABA) inhaler. If asthma is poorly controlled, one needs to review the diagnosis of asthma, medication adherence (especially inhaler technique), triggering factors (e.g., smoking, use of NSAIDs or beta blockers), and comorbid conditions (e.g., rhinosinusitis or GERD) and then consider stepping up the treatment regimen. If symptoms are well controlled for 3 months, consider stepping down, but it is strongly recommended to continue the steroid inhaler.

COPD management is summarized in Table 12.4 [10]. FEV_1 value is important to establish the diagnosis of COPD

Table 12.3 Stepwise asthma management

Reliever	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller	As needed low dose ICS-formoterol		Low-dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add LAMA Refer to asthma specialist
Reliver	As needed low-dose ICS-formoterol				
Alternate controller choice	Take low-dose ICS whenever SABA taken	Low-dose ICS maintenance	Low-dose maintenance ICS-LABA	Medium–/high-dose maintenance ICS-LABA	Add LAMA Refer to asthma specialist
Reliever	As needed SABA				

Modified from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022
ICS inhaled corticosteroid, *LABA* long-acting beta2-agonist, *SABA* short-acting beta2-agonist, *LAMA* long acting muscarinic antagonist

Table 12.4 COPD management

	mMRC 0–1 **CAT <10**	**mMRC ≥2** **CAT ≥10**
Exacerbation ≥two/year or ≥ one hospitalization	Start LAMA • If further exacerbation, LAMA + LABA or LABA + ICS	Start LAMA • If further exacerbation, LAMA + LABA or ICS + LABA • If still further exacerbation, refer to pulmonologist
0–1 exacerbation/ year and no hospitalization	Choose one from SABA, LABA, SAMA, or LAMA • If effective, continue • If ineffective, stop and change to another	Start LABA or LAMA • If symptoms persist, LABA + LAMA. Consider other cause of respiratory symptoms

Global Initiative for Chronic Obstructive Lung Disease Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2022 Report)
mMRC modified MRC dyspnea scale (Fletcher CM. BMJ 1960; 2: 1662), *CAT* COPD assessment test (Jones et al. ERJ 2009; 34: 648–54 http://www.catestonline.org), *LABA* long-acting beta-agonist, *SABA* short-acting beta-agonist, *LAMA* long-acting muscarinic antagonist, *SAMA* short-acting antimuscarinics, *ICS* inhaled corticosteroid

1. Smoking cessation
2. Assess the symptom severity and exacerbation history and select bronchodilator treatment (see table)
3. Treat comorbid conditions: Common comorbid conditions include cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer. One should actively screen and treat them appropriately in order to maximize the patient's quality of life
4. Vaccination: Vaccinate against influenza, COVID-19 and pneumococcus

(post bronchodilator FEV_1/FVC <70%), but the medication choice is strongly influenced by the degree of symptoms and the history of exacerbation. LAMA (long-acting muscarnic antagonist) is the preferred choice in many patients; it is shown to improve symptoms and quality of life and reduce exacerbation and hospitalizations and has little systemic side effects. As opposed to asthma, inhaled steroid should be used selectively in patients with COPD. ICS increases the risk of pneumonia, and the effect is limited in patients whose blood eosinophil count is low (<100/μg). None of the pharmacologic therapies are shown to slow the decline of the lung functions; smoking cessation is the only definitive treatment of COPD; patients should be strongly counseled to quit smoking. A detailed discussion of COPD therapy is beyond the scope of this chapter. Comanagement with a pulmonary specialist may be indicated in patients with advanced COPD. Pulmonary rehabilitation and oxygen therapy may be appropriate in some patients. Comorbid conditions such as cardiovascular disease, depression, and osteoporosis are very common in patients with COPD; screening and treatment of comorbidity is important.

Management of heart failure is summarized in Fig. 12.2. While cardiologists may provide many aspects of specialized care, the primary care providers should work in conjunction with cardiologists and manage comorbid conditions such as obesity, smoking, hypertension, and diabetes.

In patients with chronic heart or lung disease, the symptom of dyspnea can be challenging to manage; physical therapy may be beneficial in some cases. Oxygen therapy can be considered in select hypoxic patients. Those with advanced end-stage illness may suffer from refractory dyspnea; opiates should be considered in these situations [11].

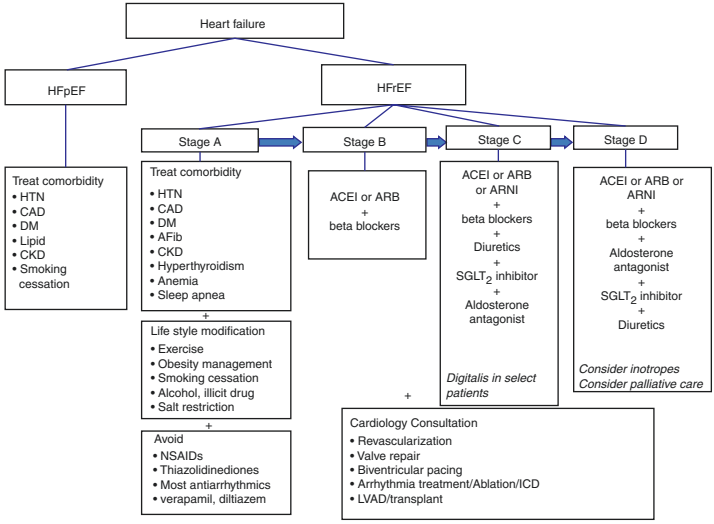

FIGURE 12.2 Heart failure management. **Stage A**: Patients at high risk for heart failure but without structural disease or symptoms. **Stage B**: Patients with structural heart disease but without signs or symptoms. **Stage C**: Patients with structural heart disease with prior or current symptoms. **Stage D**: Patients with refractory heart failure requiring specialized interventions. (1) *HFpEF* heart failure with preserved ejection fraction (EF ≥50%). (2) *HFrEF* heart failure with reduced ejection fraction (EF ≤40%). (3) *HTN* hypertension, *CAD* coronary artery disease, *DM* diabetes mellitus, *CKD* chronic kidney disease. (4) *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker. (5) *ICD* implantable cardioverter defibrillator. (6) *LVAD* left ventricular assist device. (7) *NSAIDs* nonsteroidal anti-inflammatory drugs (8) *ARNI* angiotensin receptor-neprilysin inhibitor. (Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J AmColl Cardiol. 2022;79(17):e263–e421.)

Clinical Pearls

- When the routine history and physical examination are not revealing, carefully watch how the patient walks and with what pace while monitoring pulse rate and oxygen saturation by pulse oximetry. This way the provider can get a sense of the patient's exercise capacity.

Don't Miss This!

- Viral myocarditis may present with malaise, low-grade fever, and nausea with little classical CHF symptoms; it can be misdiagnosed as viral gastroenteritis, but the patient's general appearance is usually very ill and vital signs are quite abnormal.
- Patients with angina may describe vague chest symptoms as dyspnea on exertion. Careful attention to the symptoms of chest tightness (which may or may not be typical squeezing in nature), nausea, and diaphoresis is important especially in patients with cardiovascular risk factors. If acute coronary syndrome is deemed likely, patients would be best evaluated in the emergency room.

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Chapter 13
Sinusitis or Rhinosinusitis

Shuchita Khasnavis

Abbreviations

ABRS	Acute bacterial rhinosinusitis
ARS	Acute rhinosinusitis

Introduction

Sinusitis affects about one in seven people in the USA, and nearly always occurs with inflammation of the nasal mucosa [1].

The vast majority of the cases are viral in origin, and only a small percentage is bacterial. Most of the cases resolve with conservative treatment, and a few require antimicrobials [2].

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The four sinus cavities and their locations are detailed below:

- Frontal sinuses: behind the forehead and part of the frontal bones
- Maxillary sinuses: behind the cheek bone
- Ethmoid sinuses: behind the nasal passages
- Sphenoid sinuses: near the optic nerve and part of the orbits (Fig. 13.1)

Sinusitis occurs if obstruction or congestion blocks the paranasal sinus opening thereby causing mucus to build up in the chamber. This blockage allows bacteria and viruses to multiply leading to infection and inflammation.

Symptoms of sinusitis include the following:

- Thick nasal discharge
- Facial pain or pressure
- Fever
- Reduced sense of smell

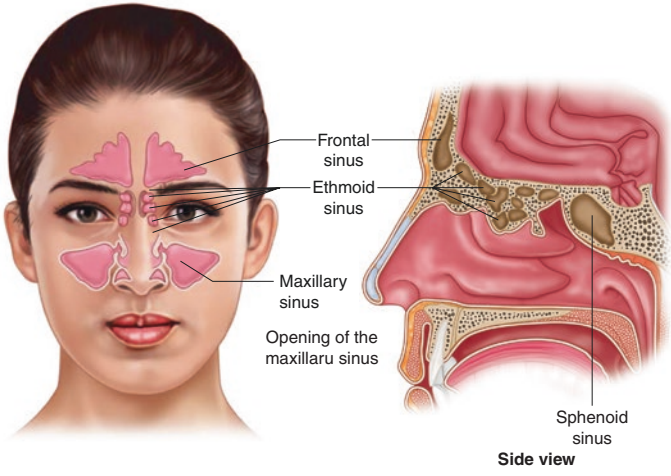
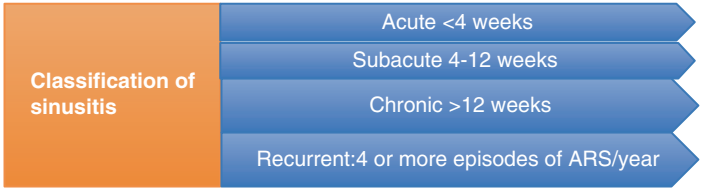


Figure 13.1 Paranasal sinus anatomy

Depending on how long these symptoms last, sinusitis is classified as acute, subacute, chronic, or recurrent [3, 4].

- Acute sinusitis: inflammation of sinuses lasting less than 4 weeks.
- Subacute Sinusitis: inflammation and infection of the sinuses lasting between 4 and 12 weeks.
- Chronic sinusitis: infection of the sinuses lasting at least 12 weeks or recurrence of infection.
- Recurrent sinusitis: four or more episodes of ARS/year with interim symptom resolution.



Acute Sinusitis

Etiology of ARS [4, 5]:

- Ninety to ninety-eight percent of sinusitis is secondary to viral infection. In the vast majority of cases, the cause is a viral upper respiratory tract infection such as the common cold.
- Bacterial sinusitis occurs in 0.5–2% of episodes of ARS.

The most common organisms are as follows:

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- Moraxella
- *Staph aureus*
- Anaerobes

- Other rare causes of ARS are fungi, allergies, or autoimmune reactions. Fungal rhinosinusitis, the majority of which are Aspergillus, tend to occur in people who are immunosuppressed.

ARS is divided into uncomplicated and complicated [3, 6]:

Uncomplicated: when infection and inflammation occur without extension beyond the paranasal sinuses.

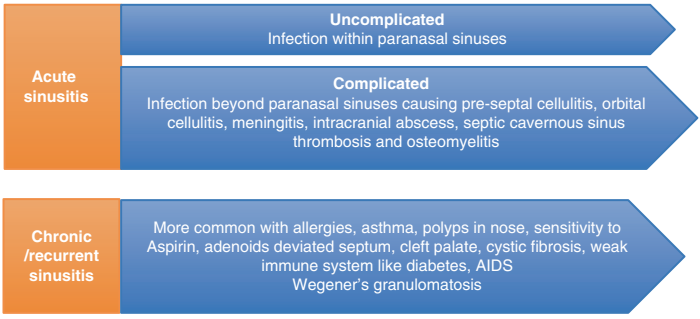
Complicated: when infection extends beyond the paranasal sinuses leading to involvement of surrounding structures and causing one of the following:

- Preseptal cellulitis
- Orbital cellulitis
- Subperiosteal abscess
- Meningitis
- Intracranial abscess, epidural abscess
- Osteomyelitis
- Septic cavernous sinus thrombosis

Chronic/Recurrent Sinusitis

Allergies and asthma are two of the conditions most commonly seen in patients with chronic or recurrent sinusitis. Seasonal allergies and rhinitis may cause blockage and predispose to sinusitis. The risk of sinusitis is higher with severe asthma. People with a combination of polyps in the nose and sensitivity to aspirin are at high risk for recurrent or chronic sinusitis. Chronic sinusitis and recurrent sinusitis are also associated with disorders that weaken the immune system such as diabetes, AIDS, cystic fibrosis, and Wegener's granulomatosis. Structural abnormalities of the nose such as polyps, enlarged adenoids, cleft palate, tumors, and deviated septum can lead to the blockage of nasal passages and mucous drainage. Some hospitalized patients with head injuries, nasal tubes, mechanical ventilators, and weakened immune systems are at higher risk for sinusitis.

Other medical conditions affecting sinuses include gastroesophageal reflux, oral or intravenous steroid treatment, hypothyroidism, and Kartagener's syndrome. Miscellaneous risk factors are dental problems, change in pressure while flying, high altitudes, swimming, smoking, and air pollution.



Symptoms of Acute Sinusitis

General symptoms of acute sinusitis (both viral and bacterial) [7] include the following:

- Purulent anterior and posterior nasal discharge
- Nasal congestion or obstruction
- Facial congestion, fullness and pain
- Anosmia
- Fever
- Headache
- Ear pain, pressure, and fullness
- Halitosis
- Dental pain
- Fatigue

In general, viral sinusitis symptoms last 7–10 days.

- Covid-19 infection may present with symptoms of acute sinusitis. Overlapping symptoms can make it difficult to determine the nature of infection. While both can cause fever, headache, nasal congestion, and sore throat, there are some differences between the two. Covid-19 causes more of a dry cough and loss of taste and smell, typically more respiratory symptoms, and fatigue.

Symptoms of Chronic Sinusitis

Symptoms of chronic sinusitis are more vague. The fever may be low grade or absent. The symptoms last at least 12 weeks or are intermittent throughout the year [8, 9].

Physical Findings

Patient with sinusitis usually present with erythema, edema, or tenderness over the involved sinus [10].

- Maxillary sinusitis: The cheek is tender, or the patient may present with jaw pain and tooth sensitivity.
- Frontal sinusitis: Pain on palpation of the forehead.
- Ethmoid sinusitis: Swelling and tenderness in the eyelids and surrounding tissue.
- With any sinusitis the pain and tenderness may be found in several locations. Purulent nasal discharge may be evident on examination. Diffuse mucosal edema and inferior turbinate hypertrophy may be found.

Diagnosis

In the primary care setting, a thorough history and physical examination can provide reliable diagnosis of acute sinusitis [11]. Differentiation from common viral upper respiratory tract infection is important where nasal congestion is predominant without head congestion and facial pains. The presence of purulent secretions has the highest positive predictive value for clinically diagnosing sinusitis (Fig. 13.2).

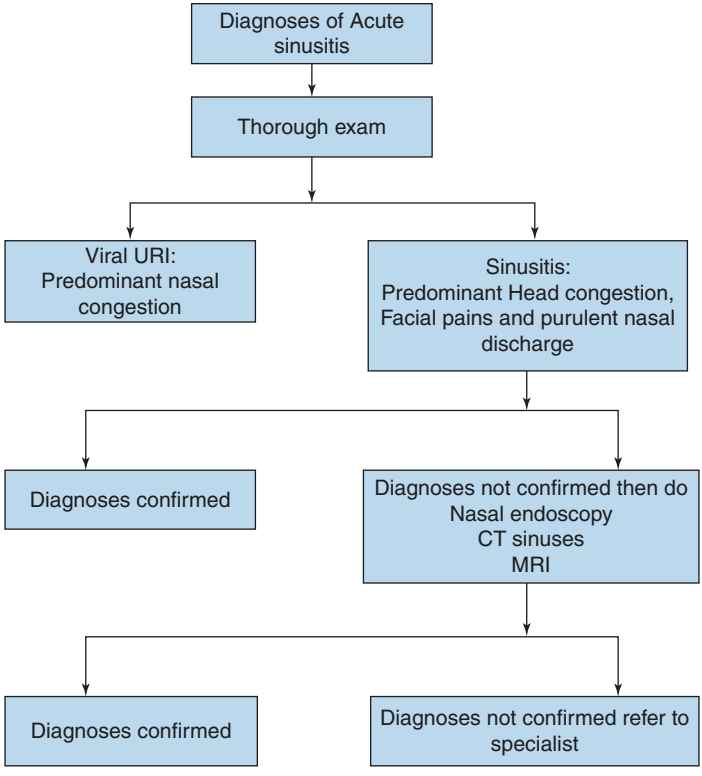


Figure 13.2 Diagnostic algorithm for acute sinusitis

Diagnostic Tests

Since the diagnosis can often be made based on history and physical examination, testing is done when the clinical diagnosis is uncertain.

- *Nasal endoscopy* or rhinoscopy allows detection of abnormalities of the nasal passage, polyps, and pus. Bacterial culture can be taken from samples.
- *Imaging techniques*
  - CT scan is the best method for viewing paranasal sinuses and reveals the extent of inflammation and disease.
  - X-ray is not as accurate as CT and is used when CT scan and endoscopy are unavailable.
  - MRI is not as effective as CT and is more expensive. It may be used to differentiate between inflammatory disease, malignant tumors, and complications within the skull.
- *Sinus puncture and bacterial culture* is a standard reliable method for making the diagnosis. Due to the invasive nature of this process, it should be reserved for those patients that have not responded to antibiotics or those at risk of having an unusual infection or serious complications.

Treatment of Acute Sinusitis

The primary objective for treatment of sinusitis is reduction of swelling, eradication of infection, and drainage of sinuses. The majority of cases will resolve with supportive care, and few, 2–10%, of acute rhinosinusitis will require antimicrobials [11, 12].

Treatment can be divided into the following categories:

- Immunocompetent patients with good follow-up: Supportive treatment with saline irrigation, steam inhalation, and hydration along with medications such as nasal or oral decongestants, antihistamines, and mucolytics are effective. Symptoms usually resolve in 7–10 days.

The decision to use antibiotic therapy for acute bacterial sinusitis is based on how symptoms present or progress. Symptoms favoring treatment include the following:

- Duration of 7–10 days
- High fever (>102)
- Purulent nasal discharge
- Worsening of symptoms after conservative management
  - The choice of antibiotics should cover the following: *S. pneumonia*, *H. influenzae*, *M. catarrhalis* [12, 13].

Antibiotic treatment of choice is amoxicillin 875 mg/clavulanic acid 125 mg BID or 500 mg/125 mg TID. If resistance is suspected, then use a higher dosage of amoxicillin/clavulanic acid 2000 mg/125 mg BID.

For patients with penicillin allergy, any of these medications can be used. Doxycycline, levofloxacin, moxifloxacin, or clindamycin plus a third-generation oral cephalosporin. See treatment algorithm.

- Antibiotics should be continued for at least 5–7 days.

If there is no improvement in 72 h with initial therapy or there is worsening of symptoms, then the antibiotic should be changed. Switch to a second line therapy (second-line agent will depend on initial therapy), refer patients for imaging studies and send cultures, and consider alternative diagnoses (Fig. 13.3).

The risk factors for resistance to antibiotics are as follows:

- Age > 65
- Hospitalization in the last 5 days
- Antibiotic use in previous month
- Immunocompromised patients
- Comorbidities: diabetes, cardiac disease, renal failure, hepatic disease.
  - Severe infection, fever >102
  - Threat of suppurative complications

Immunocompromised and severe symptoms may warrant immediate antibiotics and specialist referral.

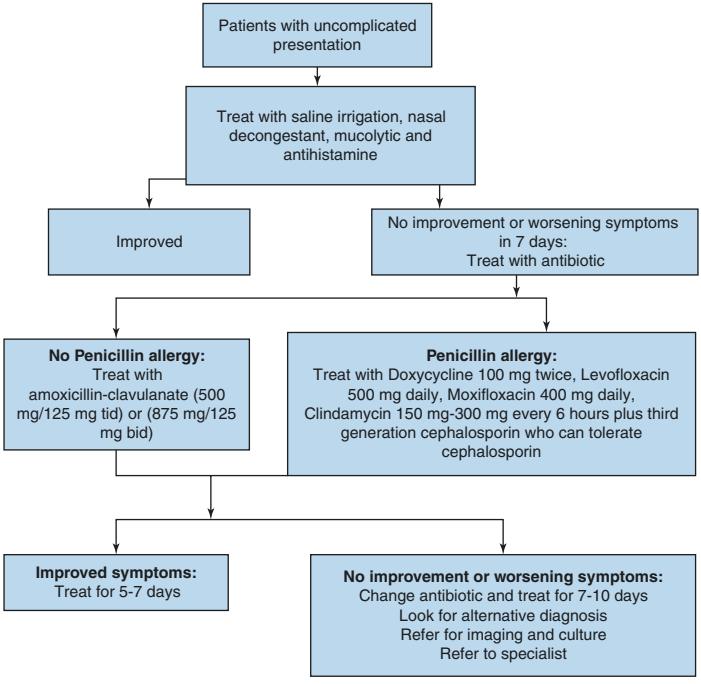


FIGURE 13.3 Treatment algorithm for acute sinusitis

Relapse Recurrence of symptoms after oral therapy within 2 weeks represents inadequate eradication of infection. If symptoms are mild, treat with the same antibiotic for a longer duration. If symptoms are severe, switch to an alternative antibiotic.

Adjunct therapy Oxymetazoline and phenylephrine hydrochloride nasal spray may be used for 3–5 days. Long-term use may cause rhinitis medicamentosa, otherwise known as rebound congestion. Intranasal corticosteroids may be beneficial.

Treatment of Chronic Sinusitis

Chronic sinusitis results from damage to the mucous membrane from past infection. The role of antibiotics is controversial unless there is a concomitant acute infection [8, 12].

- Antibiotics should be continued for 4–6 weeks and should cover organisms causing acute sinusitis and staphylococcus species and anaerobes.
- These include amoxicillin-clavulanate, cefpodoxime proxetil, cefuroxime, gatifloxacin, moxifloxacin, and levofloxacin.
- Nasal corticosteroid spray and saline irrigation may provide additional relief.
- A short course of oral steroids may be used for extensive mucosal thickening and severe congestion. If no improvement, surgery may be considered.
- Patients with allergies, sinusitis, and asthma should have treatment targeting each condition. Treatment may include nasal steroids, leukotriene antagonists, antihistamines, and immunotherapy.

Additional Evaluation

Laboratory evaluation may be necessary to look for an underlying disorder. Lab tests may include sweat chloride test for cystic fibrosis, ciliary function test, HIV, and immunoglobulin testing. Any patient with recurrent sinusitis should have an allergy consultation.

Emergency treatment Patients with fungal sinusitis or signs of infection spreading beyond the paranasal sinuses (e.g., to the brain or bone) need urgent treatment with parenteral antibiotics and surgery.

Prevention The best way to prevent sinusitis is to practice good hand hygiene and obtain influenza and pneumococcal vaccines as per recommendations.

Clinical Pearls [14]

Acute sinusitis is viral in nature in the vast majority of cases and usually resolves in 7–10 days without treatment.

- The presence of purulent secretions has the highest positive predictive value for clinically diagnosing sinusitis.
- The antibiotic of choice without penicillin allergy is amoxicillin/clavulanate.
- CT of sinuses is the imaging procedure of choice.

Do Not Miss!

- Patients with immunocompromised conditions and severe symptoms may need immediate attention, imaging studies, and antibiotic treatment to prevent extension of infection.

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Chapter 14
Sore Throat

Lori Ciuffo

Introduction

Acute pharyngitis is one of the most common conditions in patients presenting with a sore throat.

Approximately 12 million ambulatory care visits in the USA present with a sore throat [1]. It is characterized by inflammation of the pharynx, nasopharynx, and tonsillar tissue. Incidence peaks between late winter and early spring. Eighty percent of cases are caused by viral agents, and the remaining are bacterial and rarely, fungal infections [2].

Among the many viruses, up to 20% of patients with Covid-19 present with a sore throat [1, 3].

Strep throat and COVID-19 can produce many of the same symptoms including fever, headache, body aches, and vomiting. A few distinctions between them are strep throat causes pain when swallowing, tonsillar exudates, petechiae, and swollen lymph nodes.

Strep throat, caused by bacterial infection from *Streptococcus*, requires antibiotics to prevent nonsuppurative

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complications including rheumatic fever and glomerulonephritis and suppurative complications including bacteremia, cervical lymphadenitis, endocarditis, mastoiditis, meningitis, otitis media, peritonsillar and retropharyngeal abscess, and pneumonia [4, 5].

Decision-Making/Differential Diagnosis

All patients with acute pharyngitis should be tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with a sensitive reverse-transcriptase polymerase chain reaction (PCR) test. This is to identify patients who are infectious and to isolate and perform contact tracing [2].

Viruses including adenovirus, influenza virus, parainfluenza virus, rhinovirus, and respiratory syncytial virus are frequent causes of acute pharyngitis. Other viral agents include coxsackievirus, echovirus, coronavirus, enterovirus, cytomegalovirus (CMV), human immunodeficiency virus (HIV), and herpes simplex virus. The Epstein-Barr virus is a frequent cause of acute pharyngitis accompanied by other clinical features of infectious mononucleosis such as generalized fatigue, lymphadenopathy, and splenomegaly. Systemic infections with rubella virus or measles virus can be associated with acute pharyngitis [6, 7]. Other bacterial causes of acute pharyngitis include *groups C* and *G beta-hemolytic streptococci*, *Corynebacterium diphtheria*, *Arcanobacterium haemolyticum*, *Neisseria gonorrhoeae*, *Chlamydia pneumoniae*, *Francisella tularensis*, *Fusobacterium necrophorum*, and *Mycoplasma pneumoniae*.

Noninfectious causes include irritants such as cigarette smoking or second-hand exposure, dry air, allergic rhinitis or sinusitis, gastroesophageal reflux disease, trauma caused by intubation or straining as with shouting, medications including angiotensin-converting enzyme inhibitors, and some chemotherapeutics, autoimmune disorders including Kawasaki disease and Bechet syndrome [2].

It is important to distinguish between the two most common infectious etiologies of acute pharyngitis because management strategies differ [1].

1. Respiratory viruses
2. *Group A streptococcus* (GAS)

Red flags and the need for urgent care: Upper airway obstruction can result from severe pharyngeal inflammation but is more commonly associated with infectious mononucleosis and invasive infections involving the deep tissue of the neck. Signs of upper airway obstruction include a muffled or "hot potato" voice, hoarseness, drooling or pooling of saliva, stridor, respiratory distress (tachypnea, dyspnea, retractions), and "sniffing" or "tripod" positions which help maintain airway patency [5].

Key H&P

History of exposure to strep pharyngitis with exam findings including pharyngeal erythema, fever, tonsillar exudates, tender, and enlarged anterior cervical lymph nodes, and palatal petechiae is highly suspicious of GAS. Lymphadenopathy in any area other than the anterior cervical chain is not typical of GAS but is common in mononucleosis. The presence of a rash should be noted, and signs and symptoms of conjunctivitis, coryza, cough, diarrhea, hoarseness, and stomatitis are highly suggestive of viral infection as stated above [5, 6].

Viral pharyngitis clinical features include cough, nasal congestion, conjunctivitis, coryza, oral ulcer, and viral exanthem.

Antibiotic treatment is recommended for patients with GAS pharyngitis, and supportive care is sufficient for patients with viral pharyngitis.

*Modified Centor score (*Fig. 14.1*) and FeverPAIN score (*Fig. 14.2*) can be used to identify patients at low, moderate, and high risk of group A strep pharyngitis.*

Absence of cough	*1*
Swollen tender anterior cervical nodes	*1*
Temperature >100.4 F	*1*
Tonsillar exudates or swelling	*1*
3-14 years of age	*1*
14-44 years of age	*0*
45 years or older	*-1*

Total Score	***risk of GAS***	***Recommendation*** (#7)
Score = 0	*1-2.5%*	*No further testing or antibiotic needed*
Score=1	*5-10%*	*Option to perform RADT or culture*
Score=2	*11-17%*	*strep testing / culturetreat if rapid test positive*
Score=3	*28-35%*	*strep testing / culturetreat if rapid test positive*
Score= ≥ 4	*51-53%*	*No further testing, treat empirically*

FIGURE 14.1 Modified Centor score

FeverPAIN Score for Pharyngitis	**Points**
Fever in past 24 hours	*1*
Intensely inflamed tonsils	*1*
Presentation within 3 days of symptom onset	*1*
Purulent tonsils	*1*

Points	*Risk*	***Recommendation***
0 or 1	*1 to 10%*	*No testing or treatment, consider backup throat culture In children 3-15 years of age*
2	*11 to 17%*	*Rapid antigen detection testing*
3	*28 to 35%*	*Rapid antigen detection testing*

FIGURE 14.2 FeverPAIN score for pharyngitis

Rapid Antigen Detection Tests

Because of improvements in the sensitivity of the rapid antigen detection test, a negative result no longer have to be confirmed by a throat culture [8], sensitivity 91% and specificity 93% [9].

Using throat culture to confirm negative RADT is reserved for patients who are at higher risk for severe infection or complications, patients in close contact with individuals at high risk for complications, patients living in college dormitories or other settings, and patients living in an area where acute rheumatic fever is endemic [1].

Treatment

Group A strep pharyngitis is self-limited and resolves without treatment; however, treatment (Figs. 14.3 and 14.4) is to prevent complications which include *suppurative* (bacteremia, cervical lymphadenitis, endocarditis, mastoiditis, meningitis, otitis media, peritonsillar/retropharyngeal abscess, and pneumonia) and *nonsuppurative* (poststreptococcal glomerulonephritis and rheumatic fever).

Sulfonamides, fluoroquinolones, and tetracyclines have a high rate of resistance and failure to eradicate the organisms from the pharynx.

Patients with GAS generally improve within 3–4 days and are no longer contagious after 24 h of antibiotics.

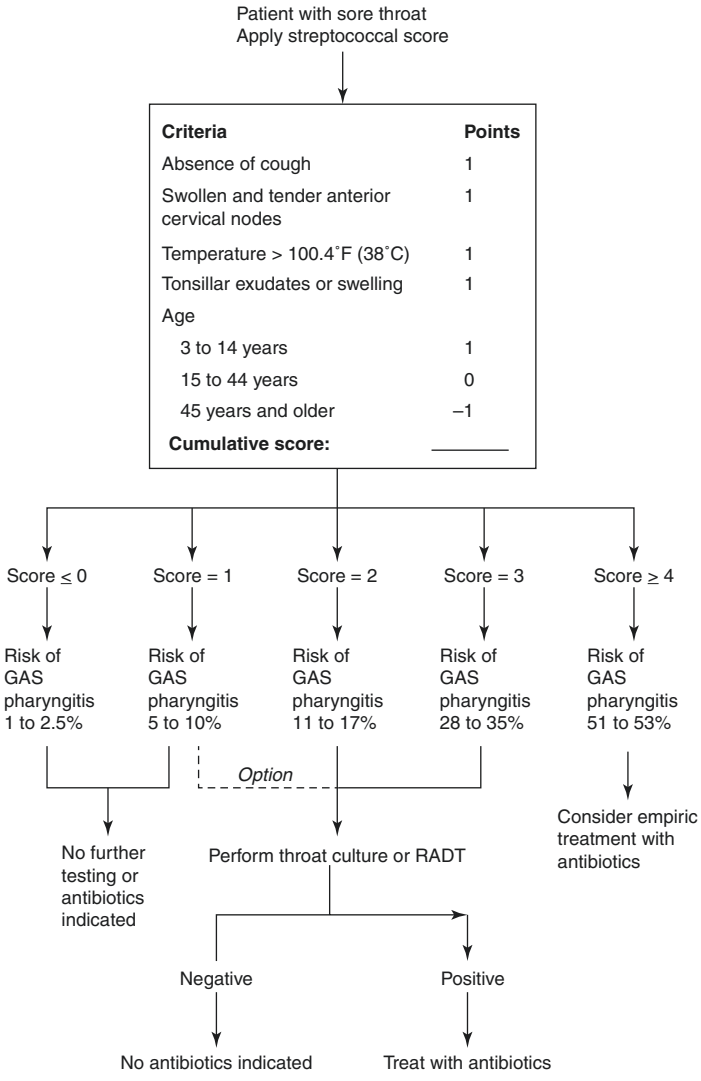

FIGURE 14.3 Modified Centor score and management options using clinical decision rule. Other factors should be considered (e.g., a score of 1, but recent family contact with documented streptococcal infection). *GAS group A beta-hemolytic streptococcus*, *RADT* rapid antigen detection testing [7, 12]

Antibiotic Options for Group A Strep pharyngitis (#1, #4, #8, #13# 14)

Drug	Class of Antimicrobial	Route of Administration	Dosage	Duration
Penicillin	Penicillin	PO	500 mg bid	10 days
Penicillin G benzathine	Penicillin	IM	1,200,000 Units	x 1 dose
Amoxicillin	Broad Spectrum Penicillin	PO	500 mg bid	10 days
Cephalexin	Cephalosporin	PO	500 mg bid	10 days
Clindamycin	Lincomycin	PO	300 mg tid	10 Days
Clarithromycin	Macrolide	PO	250 mg bid	10 Days
Azithromycin mg xdays 2-5	Macrolide	PO	500 mg x day 1 followed by 250	

FIGURE 14.4 Antibiotic options for *group A strep pharyngitis* [1, 4, 9–11]

Symptomatic Treatment

Systemic oral therapy is effective at reducing the pain of acute pharyngitis. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) remain the two most studied. NSAIDs appear to be more effective than acetaminophen. Topical therapies are an alternative for patients who are at higher risk for side effects from it. The use of glucocorticoids for the treatment of sore throat pain is generally not suggested due to the potential for serious side effects compared with the slight reduction in the duration of sore throat pain [12].

Clinical Pearls

- Use the modified Centor Score to guide testing.
- Rapid antigen detection tests should be reserved for concern about starting antibiotics [6].
- Throat culture remains the standard for bacterial pharyngitis [6].
- Empirical antibiotic use should be limited to patients who are severely ill and no improvement within 5 days of presentation.

- Red flags include rigors, inability to swallow, stridor, muffled voice, respiratory distress, and tripod position.

Don't Miss This

- Evaluate for serious complications in patients presenting with drooling, dysphonia, muffled voice, and neck swelling.

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Chapter 15
Sleep Apnea

Jhansi Nalamati and Dushyant Damania

Introduction

Sleep disorders are very common in the primary care setting. Sleep deficiency/deprivation is a common health problem in the United States. Prevalence of obstructive sleep apnea (OSA) is estimated to be around 3% among women and 10% among men 30–49 years of age; and 9% among women and 17% among men 50–70 years of age, with approximately ~24 million undiagnosed [1–3]. Based on the International Classification of Sleep Disorders (ICSD-3), insomnia is the most common sleep disorder in the general population followed by sleep-disordered breathing, including obstructive sleep apnea/hypopnea syndrome and central sleep apnea [4].

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ICSD3 Classifies Sleep Disorders into Seven Major Categories [4]

1. Insomnia
2. Sleep-disordered breathing disorders
3. Central disorders of hypersomnolence
4. Circadian rhythm sleep-wake disorder
5. Parasomnias
6. Sleep-related movement disorder
7. Other sleep disorders

Sleep apnea is classified as obstructive sleep apnea/hypopnea syndrome (OSAHS) and central sleep apnea (CSA).

Prevalence

Obstructive sleep apnea prevalence varies widely, with 9–38% having OSA (AHI 5 events/h). It is also seen more in men and in the elderly. Moderate to severe forms of OSA with an apnea-hypopnea index (AHI of 15 events/h) in the general population ranged from 6 to 17% and as high as 49% with advanced age [5].

Sleep History

In addition to general medical, surgical, family, caffeine intake, and medication history (specifically herbal remedies or over-the-counter medications), the focused sleep history should include a general question about excessive daytime sleepiness (EDS) or fatigue (including history of sleepiness while driving and accidents), difficulty falling asleep at night or maintaining sleep, sleep latency, snoring, nocturnal awakenings, witnessed apneas, sleeping position (lateral, supine, or prone), resuscitative snorts, restless legs, limb movements (noted by the partner), bedtime, wake time, daytime naps, sleep paralysis, and cataplexy.

Screening Questionnaires to Assess the Risk of OSA

Commonly used questionnaires to assess the risk of OSA are the Epworth sleepiness score with STOP-Bang questionnaire [6, 7].

STOP-Bang Questionnaire

S	Snoring
T	Tired or sleepy
O	Observed apneas
P	Pressure (hypertension)
B	BMI >35
A	Age >50 years
N	Neck circumference >16 in. in men and 15 in. in women
G	Gender: Male

0–2, low risk of OSA; **3–4**, moderate risk of OSA; and **5–8**, high risk of OSA

Adapted from Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. Br J Anaesth. 2012 May;108(5):768–75. https://doi.org/10.1093/bja/aes022. Epub 2012 Mar 8. www.stopbang.ca

Epworth sleepiness score (ESS) is the most widely used in clinical practice to evaluate the severity of sleepiness. Developed by Murray Johns at Epworth Hospital in Melbourne, Australia, this validated an eight-item questionnaire about the person's chance of dozing in differing circumstances. Dozing probability is designated as none (0), slight [1], moderate [2], or high [3] for eight situations [8], which are sitting and reading, watching TV, sitting inactive in a public place, being a passenger in a car for an hour, lying down in the

afternoon, sitting and talking to someone, sitting quietly after lunch with no alcohol, and stopping for few minutes in traffic while driving.

Understanding ESS Score

0–10	Normal range in healthy adults
11–14	Mild sleepiness
15–17	Moderate sleepiness
18 or higher	Severe sleepiness

Focused Physical Exam

Attention should be paid to the pharyngeal examination. Increased BMI is a risk factor for OSA, especially when associated with short neck or increased neck circumference. Overall, narrowed pharyngeal space, in addition to enlarged tonsils and adenoids, increases the risk of OSA. Craniofacial abnormalities also increase the risk of obstructive sleep apnea/hypopnea syndrome (OSAHS), as do abnormalities associated with reduced pharyngeal space [9].

OSA/SDB (Obstructive Sleep Apnea/Sleep-Disordered Breathing)

Definition

OSA is defined by repetitive complete obstruction (apnea) or partial obstruction (hypopnea) of the collapsible part of the upper airway during sleep [10]. Apnea or hypopnea is cessation of breathing or decreased breathing for 10 s, associated with oxygen desaturation of at least 3% and followed by an arousal (Fig. 15.1). Hypopnea is defined by the decrease in airflow by 30–50%, associated with at least 3% oxygen desaturation, followed by an arousal. AHI is the sum of apneas and

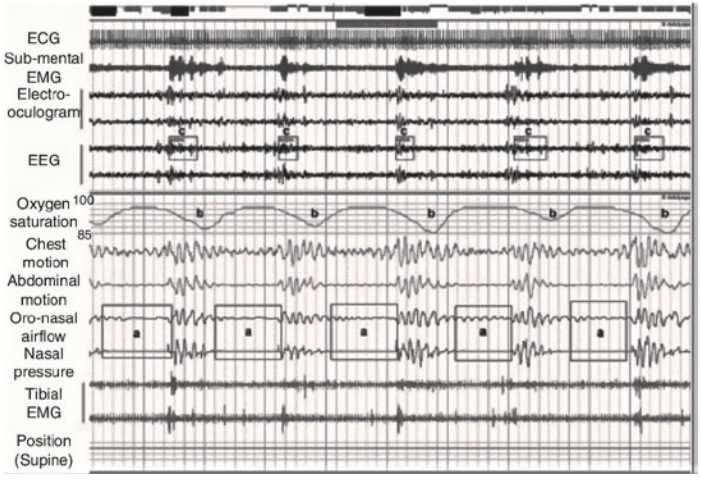

FIGURE 15.1 Five-minute epoch of supine stage II sleep in a subject with severe OSA. Cessation (apnea) in breathing (**a**) result in arterial oxygen desaturation (**b**) and EEG arousal from sleep (**c**). Chest wall motion continues during the apneas indication that the events are due to upper airway obstruction [11]

hypopneas per hour of sleep. Respiratory disturbance index (RDI) is also used interchangeably with AHI.

Primary snoring is defined by normal AHI with snoring. Ninety-four percent of patients with OSA have snoring. Classically, the three clinical features of OSA are loud snoring, witnessed apneas, and excessive daytime sleepiness. Sleep apnea is classified as mild (AHI 5–15 per hour of sleep), moderate (AHI 15–30 per hour of sleep), and severe (AHI >30 per hour of sleep).

Risk Factors

Risk factors include male sex, obesity, large neck circumference, narrowed pharynx or airway, certain craniofacial abnormalities, family history, postmenopausal women, smoking, chronic gastroesophageal reflux disease (GERD), and other chronic medical conditions including CHF, ESRD, chronic

lung disease (asthma, COPD, and IPF), stroke/TIA, acromegaly, hypothyroidism, PCOS, and pregnancy. Seventy-five percent of individuals with OSA have underlying obesity [12].

Pathophysiology

Obstructive sleep apnea is characterized by recurrent functional collapse of the pharyngeal airway, causing reduced or cessation of airflow with ongoing effort to breathe. This leads to intermittent hypoxia and disturbed sleep, leading to nonrestorative sleep. Upper airway collapse is worse in REM sleep. In obese individuals, it is hypothesized that large deposits of fat in the neck cause the upper airway to collapse in the supine position during sleep. Clinical features of OSA and SDB (sleep-disordered breathing) include loud snoring, nocturnal choking with resuscitative snorts, witnessed apneas, EDS, fatigue, poor concentration, morning headaches, nocturnal polyuria, and nocturnal angina. Most of the symptoms are related to disruption of normal sleep architecture. Patients have associated obesity, increased neck circumference, greater than 17 in. in men and greater than 15 in. in women, hypertension, metabolic syndrome, and anatomic abnormalities. Recent studies showed progesterone stimulation of upper airways muscles of ventilation may contribute to lower prevalence of OSA in pre-menopausal women than older women, whereas higher androgen level (use of androgen supplement or patients with PCOS) may increase muscle mass in the tongue and worsen OSA [13].

Diagnosis

Usually nocturnal polysomnography (PSG) in a center or out-of-center sleep testing (OCST), which is also called at home sleep testing (HST), helps diagnose OSA (see Fig. 15.2). However, recently peripheral artery tonometry has utility in screening OSA [14].

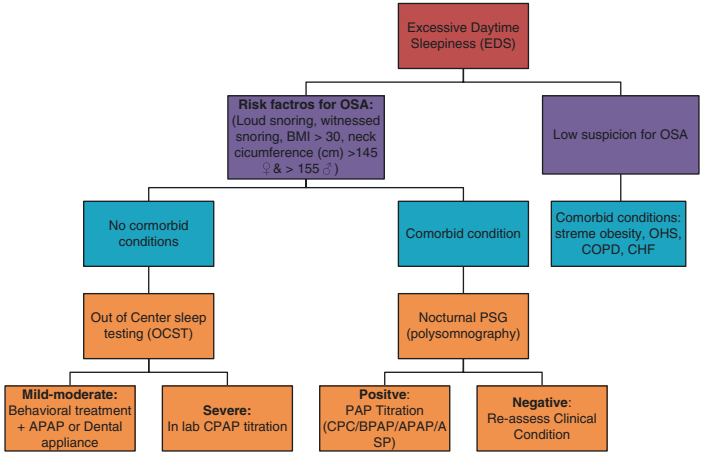

FIGURE 15.2 Evaluation of excessive daytime sleepiness

Differential Diagnosis of Excessive Daytime Sleepiness (EDS)

Other conditions that lead to EDS are depression, chronic sleep deprivation, restless legs syndrome (RLS), periodic limb movement disorder (PLMD), narcolepsy, shift work sleep disorder, and jet lag.

Complications and Consequences of Untreated Sleep Apnea

There is increasingly more data to suggest that untreated sleep apnea is associated with metabolic syndrome, poor cardiovascular outcomes, HTN, and congestive heart failure [15, 16]. Recent data, however, states that CPAP may not lead to a significant decrease in morbidity [6]; EDS is also associated with increased risk for injuries and motor vehicle accidents. Patients may have poor concentration and memory lapses leading to poor quality of life.

Treatment: OSAHS/SDB (Usual Therapy)

- Behavioral treatment: Weight loss and sleep hygiene
- Positive airway pressure (PAP), CPAP, BPAP, and ASV [17]
- Surgery (effective for mild OSA): uvulopalatoplasty when if indicated is effective for primary snoring with or without mild OSA [18]
- UPPP (uvulopalatopharyngoplasty) and MMA (maxillomandibular advancement)
- Laser-assisted uvulopalatoplasty (LAUP) and radiofrequency ablation
- Hypoglossal nerve stimulation (moderate to severe OSA) [19]
- Hyoid surgery: Hyothyroid opexy and hyoid myotomy with suspension
- Dental appliances (oral appliance therapy)

The most effective treatment and first-line therapy is continuous positive airway pressure (CPAP) [17]. With new masks, complications and adverse effects are low; however, there is a high incidence of intolerance to the mask or pressure in patients with claustrophobia and anxiety disorders. Common complaints include oropharyngeal dryness, mask leak and fit, redness and excoriation of the facial skin, stomach bloating, and ear fullness. CPAP titration is recommended in all patients with comorbid conditions, like COPD, CHF, and OHS. Eight percent of patients have combined OSA with CSA.

Other treatments include medical and behavioral therapy with weight loss, bariatric surgery, and positional treatment. Supplemental oxygen, nasal decongestants, protriptyline, and SSRIs, however, have limited utility. These are more effective measures for mild to moderate OSA and as adjunctive treatment for all patients with OSA.

Modafinil is recommended to treat residual excessive daytime sleepiness in OSA patients, who have sleepiness despite effective PAP treatment [20].

Positional sleep apnea: There is 50% reduction in AHI during non-supine sleep in relation to supine sleep. These patients benefit from positional therapy.

Surgical treatment: The most commonly used nonsurgical device/oral appliance therapy for treatment of mild to moderate OSA is the dental appliance. Outcomes following pharyngeal surgeries were less consistent, and adverse effects were more commonly reported. Hypoglossal cranial nerve stimulation via an implantable neuro-stimulation system has been shown to be effective in moderate OSA to severe OSA according to a recent study [21].

The STAR trial showed that upper airway stimulation is an effective therapy for moderate to severe OSA in patients who fail PAP therapy or unwilling to use PAP [19].

Drowsy driver syndrome and commercial drivers and pilots: Untreated or undiagnosed OSA can lead to drowsy driving syndrome and lead to fatal accidents. The National Highway Traffic Safety estimates drowsy driving leads to at least 6000 fatal crashes every year [22]. In addition to OSA, chronic sleep deprivation with underlying OSA can worsen EDS. Shift work sleep disorder (circadian rhythm type) and medications that can cause sleepiness can exacerbate EDS.

Warning signs of drowsy driving include yawning or blinking frequently, difficulty remembering the past few miles driven, missing an exit, driving away from the lane, and hitting the rumble strap on the side of the road. Drivers must be educated about not driving until CPAP is effectively instituted (nightly CPAP at least 4 h in 1 week). Sometimes testing by the maintenance of wakefulness test is required to document that sleepiness resolved with treatment. The National Transportation Safety Board has specific guidelines for diagnosis and treatment of OSA in commercial drivers.

Central disorders of hypersomnolence: This includes central sleep apnea (CSA), Cheyne-Stokes breathing, and narcolepsy. CSA is common in patients with neurological conditions or with CHF. CSA is characterized by lack of drive to breathe during sleep, resulting in decreased ventilation and compromised gas exchange. In contrast to OSA, in which ongoing respiratory efforts are present, CSA is characterized by lack of respiratory effort during cessation of airflow. However, considerable overlap exists in the pathophysiology and pathogenesis of OSA and CSA [23].

Symptoms of CSA include frequent nighttime awakenings, EDS, and increased risk of adverse cardiovascular complications. Unstable ventilator drive during sleep is a principal underlying feature.

Common types of CSA include the following:

- Idiopathic CSA
- Narcotic-induced central apnea
- Obesity hypoventilation syndrome (OHS)

Prevalence of CSA: The prevalence of CSA varies considerably but is less common than OSA. A prospective prevalence study of patients with heart failure and LVF <45% reported 37% of patients had CSA [24].

Pathophysiology: Again, there is a great overlap between CSA and OSA, and typically CSA is considered the primary diagnosis when 50% of the apneas are scored as central in origin (more than 10-s cessations of breathing in the absence of respiratory effort) (Fig. 15.3).

CSA syndromes can be classified into two groups (as per wakefulness CO2 levels): hypercapnic and non-hypercapnic. Hypercapnic CSA can be classified broadly into abnormal central pattern generator output (will not breathe) or impairment of respiratory motor output caudal to respiratory generator (cannot breathe).

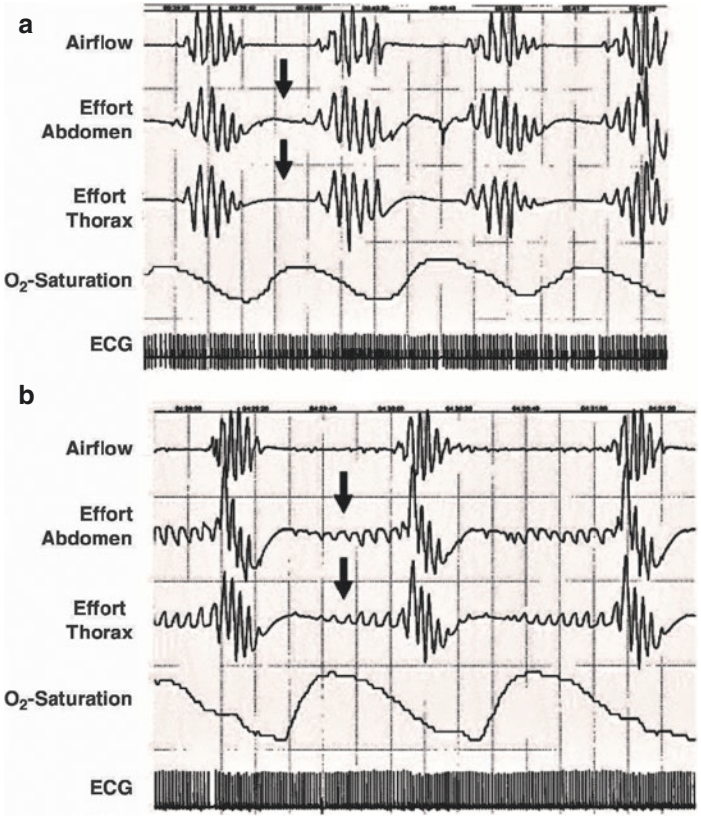

FIG. 15.3 Polysomnography (3 min) with central sleep apnea (**a**) and obstructive sleep apnea (**b**). Note the absence of chest efforts and abdominal movements in the absence of oronasal airflow in central sleep apnea but not in obstructive sleep apnea (*arrows*). Also, note the pronounced decrease in O2 saturation following each apnea episode [25]

Treatment of CSA

- Twenty percent of CSA resolve spontaneously and by treatment of underlying condition, CHF, and renal failure
- Weight loss
- Avoid sleep deprivation
- Avoid alcohol and sleep promoting agents like benzodiazepines
- CPAP is used as first-line therapy
- Adaptive servo ventilation (ASV) like CPAP provides additional ventilator support based on breath by breath analysis
- Supplemental oxygen: May not be superior to PAP but better tolerated
- Addition of dead space ventilation with CPAP
- Inhalation of carbon dioxide
- Acetazolamide or theophylline
- Overdrive atrial pacing

Obesity hypoventilation syndrome is increasing in prevalence in the developed countries, ranging from 10 to 20%; 50% of patients with BMI greater than 50 are likely to have OHS.

OHS is defined as BMI >30, PaCo2 >45 mmHg, and FEV1/FVC ratio greater than 60% on pulmonary function testing. The triad of obesity, hypersomnolence, and awake hypercapnia in the absence of alternative neuromuscular, mechanical, or metabolic explanation for hypoventilation are the cornerstone for diagnosis. Eighty to ninety percent of patients with OHS have OSA with upper airway obstruction [26].

*Narcotic-induced sleep-disordered breathing***:** Narcotics have been increasingly used for treatment of chronic pain, and a clear link between narcotic use and sleep-disordered breathing has been established. Several studies have shown

the efficacy of noninvasive ventilation, particularly ASV (adaptive servo ventilation) in improving outcome measures of central apnea index [27].

Narcolepsy: Narcolepsy is a central cause of hypersomnia and a neurological disorder that affects sleep and wakefulness. In addition to excessive daytime sleepiness, it also causes "sleep attacks," cataplexy (muscle paralysis), and sleep-onset REM sleep (SOREM). It is underdiagnosed and therefore undertreated. Although the definite cause is unknown, it may be due to deficiency of hypocretin [28].

*Circadian rhythm sleep-wake disorder***:** This group includes delayed sleep phase syndrome, advanced sleep phase disorder, jet lag, and shift work sleep disorder [29].

Parasomnias: These are mainly disorders of stage 3 or deep sleep and occur during the early period of sleep. Sleep walking, night terrors, and nocturnal seizures occur during this period.

Sleep-related movement disorders includes restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) which is a condition with an irresistible urge to move the legs. In the general population, prevalence varies anywhere from 1 to 5% and is twice more common in women than in men. This is a disorder of sensorimotor integration and may have genetically determined dysregulation of iron transport across the blood-brain barrier. It is common in persons with iron deficiency and worse in pregnant women and persons with Parkinson's disorder and end-stage kidney disease [30]. Although associated with periodic leg movement disorder, a nocturnal polysomnography is not indicated for the diagnosis. History and measurement of serum ferritin levels are considered sufficient.

Dopamine agonists are considered the first line of therapy, and these include pramipexole, ropinirole, and Regitine. Alpha-2 delta drugs such as gabapentin are being considered as first-line therapy. Opioids may be used as alternative therapy. Intravenous iron may be considered in refractory RLS.

Clinical Pearls

- Obstructive sleep apnea can be suspected by history and physical examination, but diagnosis and severity can only be assessed by a polysomnography or sleep study.
- Obstructive sleep apnea with no comorbid conditions can be treated with APAP (automated positive airway pressure devices).
- OSA with CHF, COPD, or OHS requires positive airway pressure titration with polysomnography.
- Special attention is to be given to commercial drivers and pilots with OSA and especially when associated with shift work sleep disorder (circadian rhythm sleep disorder).
- Individuals with BMI >50 can have underlying obesity hypoventilation syndrome, and individuals with underlying heart failure can have central sleep apneas, when positive airway pressure therapy may need frequent follow-up and consider repeat titration.
- Hypoglossal nerve stimulation and dental appliances are effective in moderate to severe of obstructive sleep apnea; however, it has not been tested in individuals with BMI >32.

Don't Miss This!

- Obstructive sleep apnea, although the commonest cause, is only one of the many causes of excessive daytime sleepiness (EDS). Do not miss other coexisting conditions like restless legs syndrome (frequent in pregnant individuals, individuals with end-stage kidney disease, patients on diuretics), narcolepsy, and the most common of all, chronic sleep deprivation.
- For circadian rhythm sleep disorders, the best shift that causes least sleep disturbance is the 4 PM–12 MN shift.

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Part IV
Cardiac

Chapter 16
Hypertension

Jitendra Barmecha

Brief Introduction

Hypertension is the most common condition seen in primary care practice. Not only is hypertension a major preventable cause of cardio-cerebrovascular morbidity and mortality, but it is also an independent risk factor for resulting end organ damage including myocardial infraction, stroke, heart failure, retinopathy, peripheral vascular disease, and end-stage renal disease aka hypertension-mediated organ damage (HMOD). Social determinants coupled with behavioral and genetic factors play an important role in the development of hypertension and its related complications.

Scope of the Problem

Annually, over 10 million deaths worldwide can be attributed to hypertension [1]. Approximately 80 million, or one in three American adults, have high blood pressure. About one in

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three American adults also have prehypertension, blood pressure numbers that are higher than normal but not yet in the high blood pressure range. Seventy-seven percent of individuals diagnosed with hypertension are using antihypertensive medications, but only 54% have their condition controlled. The prevalence of hypertension is projected to increase about 8% between 2013 and 2030. High blood pressure costs the nation over $50 billion each year. This total includes the cost of health care services, medications to treat high blood pressure, and missed days of work [2].

Based on the data provided by the American Heart Association [2], there is widespread racial and gender disparity in the prevalence of high blood pressure in the US population. In recent years, the incidence and prevalence of hypertension have increased, while rates of BP control have decreased. Rates in African-Americans are among the highest of any population in the world.

- 46% of African-American women have high blood pressure.
- 45% of African-American men have high blood pressure.
- 33% of white men have high blood pressure.
- 30% of white women have high blood pressure.
- 30% of Hispanic men have high blood pressure.
- 30% of Hispanic women have high blood pressure.

A recent analysis of the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2018 found large increases in hypertension awareness, treatment, and control (≈10%) within each race/ethnicity and sex subgroup except for Black females. Among Black females, levels of hypertension awareness, treatment, and control increased between 1999–2002 and 2007–2010 but decreased between 2007–2010 and 2015–2018 [1].

History and Review of Systems

Contributing factors to elevated blood pressure need to be assessed during an initial visit and for all ongoing encounters. Every clinical encounter requires a review of system and fam-

ily history of symptoms of cardio-cerebrovascular diseases, renal disease, diabetes, dyslipidemia, and gout. History of symptoms suggestive of secondary hypertension should be explored, e.g., weight gain, sedentary lifestyle, physical activity, and tobacco use [3]. Psychosocial and environmental factors that may elevate blood pressure like social determinants, family situation, employment status, working conditions, and education level need to be addressed. Sodium intake, alcohol use, intake of saturated fat, and cholesterol should be assessed. Medication history should include results and side effects of previous antihypertensive therapy, use of commonly prescribed over-the-counter medications, herbals, and illicit medications or recreational drugs that may raise blood pressure or interfere with the effectiveness of antihypertensive medications.

Decision-Making/Differential Diagnoses

The early stages of hypertension may have no clinical manifestations except elevated blood pressures. Primary or essential hypertension should be considered when there are consecutive elevated blood pressures, bilateral temporal throbbing headaches, and unexplained lower extremity edema.

Similar to primary hypertension, secondary hypertension usually does not have specific signs and symptoms even with elevated pressures. However, blood pressures not responding to usual medications, early onset (before age 30) or late onset (after age 55), normal BMI, no family history, and with end organ damage and/or dysfunction should be evaluated for refractory and or secondary hypertension.

Physical Examination

Physical examination either establishes the diagnosis or depicts the severity of disease. The following examination can be undertaken:

- Blood pressure measurements to detect and confirm the presence of high blood pressure
- Examination of the eyes including the fundus
  - Arteriolar narrowing
  - Arteriovenous nicking
  - Exudates, hemorrhages, and papilledema
- Examination of the neck
  - Carotid bruits
  - Distended veins
  - Enlarged thyroid gland
- Examination of the heart
  - Increased rate and size
  - Precordial heave
  - Clicks and murmurs
  - Arrhythmias
  - Third (S3) and fourth (S4) heart sounds
- Examination of the abdomen
  - Bruits and abnormal aortic pulsation
  - Enlarged kidneys
  - Masses
- Examination of the extremities
  - Diminished, delayed, or absent peripheral arterial pulsations
  - Bruits
  - Edema
- Body habitus, looking for changes associated with secondary hypertension
- Peripheral and central nervous system for ischemic changes

Measuring Blood Pressure

The accurate measurement of blood pressure remains the most important technique for evaluating hypertension [3]. The following steps are recommended when measuring blood pressure to avoid inaccuracies.

- No caffeine, exercise, or smoking for 30 min prior.
- Seated quietly for 5 min in a high back chair.
- Upper arms free of constrictive clothing.
- Both feet on floor, legs should not be crossed, and arm supported at the level of the heart.
- Cuff bladder should encircle at least 80% of the arm circumference.
- At least two blood pressure measurements per arm to obtain an average reading.
- Inflate the cuff to 20–30 mmHg above pulse extinction.
- Deflate at a rate of 2–3 mmHg/s.
- Systolic BP = onset of first Korotkoff sound.
- Diastolic BP = disappearance of Korotkoff sounds.
- Neither the patient nor the observer should talk during the measurement.

Diagnostic Studies

Baseline blood tests are recommended to identify those individuals at risk for hypertension or to obtain clues to diagnose secondary hypertension

- Electrocardiogram
- Urinalysis
- Urine for drug screen (based on the history)
- Fasting blood glucose
- Complete blood count
- Serum sodium, potassium, calcium, creatinine or eGFR (estimated glomerular filtration rate)
- Fasting lipid profile
- Thyroid-stimulating hormone (TSH)
- Optional tests: uric acid, measurement of urinary albumin excretion or albumin/creatinine ratio

Echocardiography, renal artery evaluation, or brain imaging *are not* routinely recommended.

As per recent guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA),

2020 [4], the blood pressure is categorized as normal, elevated, or stage 1 or 2 hypertension to prevent and treat high BP (Table 16.1).

The International Society of Hypertension (ISH) [5] provides the criteria for hypertension based on ambulatory and home BP values to define hypertension; these definitions apply to all adults above 18 years old. These BP categories are designed to align therapeutic approaches with BP levels (Table 16.2).

Table 16.1 Categories of blood pressure in adults[a]

Blood pressure	Systolic (mmHg)	Diastolic (mmHg)
Normal	Less than 120	And less than 80
Elevated	120–129	And less than 80
Stage 1 hypertension	130–139	Or 80–89
Stage 2 hypertension	140 or higher	Or 90 or higher

[a] Based on AHA/ACC 2017 guidelines

Table 16.2 International society of hypertension diagnostic blood pressure criteria[a]

Location and time	Systolic BP/diastolic BP (mmHg)
Office blood pressure	≥140 and/or ≥90
Ambulatory blood pressure monitoring	
24-hour average	≥130 and/or ≥80
Daytime average	≥135 and/or ≥85
Nighttime average	≥120 and/or ≥70
Home	≥135 and/or ≥85

[a] Adapted from Unger T et al., 2020, International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75:1334–1357

Clinical Quality Measure

Controlling blood pressure is part of a condition specific clinical quality measure. The Healthcare Effectiveness Data and Information Set (HEDIS) measures the percentage of adults aged 18–85 with a diagnosis of hypertension, whose most recent blood pressure reading was controlled based on the following criteria:

Age 18–59 whose BP was <140/90
Age 60–85 with a diagnosis of diabetes whose BP was <140/90
Age 60–85 without a diagnosis of diabetes whose BP was <150/90

Exclusions: Patients with end-stage renal disease (ESRD) or kidney transplant and pregnant status during the measurement year and admission to a non-acute inpatient setting during the measurement year.

Assessment

Once hypertension is diagnosed, further assessment is recommended to identify cardiovascular risk factors, and signs of hypertension-mediated organ damage.

Cardiovascular risk can be estimated using a calculator such as Framingham risk score (https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease) [6]. Based on new guidance on low ASCVD risk (atherosclerotic cardiovascular disease risk or 10-year CVD risk <10%) adults with stage 1 hypertension (BP 130–139/80–89), management can start with non-pharmacologic therapy. If BP remains uncontrolled at 3–6 months, pharmacologic therapy should be considered [7].

Treatment

The treatment of high blood pressure requires a multi-pronged approach, which includes lifestyle management, non-pharmacological, and pharmacological interventions.

Lifestyle Management

A healthy lifestyle is essential in the management of high blood pressure [8]. Healthy lifestyle choices can prevent or delay the onset of high BP and can reduce both cardiovascular risk and hypertension-mediated organ damage (HMOD). Diet, nutrient intake, and physical activity can play an important role in the prevention and treatment of blood pressure and its associated complications. Dietary modifications include weight loss, reduced salt intake, increased potassium intake, moderation of alcohol consumption, and consumption of an overall healthy dietary pattern, similar to a DASH (Dietary Approaches to Stop Hypertension) diet.

Diet: Emphasis on intake of vegetables (8–10 servings/day), fruits and whole grains, low-fat dairy products (2–3 servings/day), poultry, fish, legumes, nontropical vegetables oils and nuts, limited intake of sweets, sugar-sweetened beverages, and red meat is recommended. The following forms of diet to control hypertension are recommended:

- DASH (www.dashforhealth.com) [9] or its variant diet
- US Department of Agriculture (USDA) diet
- American Heart Association (AHA) diet

Diet counseling should take into account personal and cultural food preferences, appropriate calorie intake, and other medical conditions.

Dietary supplements: Garlic has been shown to have blood pressure-lowering property and therefore has been used as a dietary supplement to lower blood pressure.

Cocoa has a small blood pressure-lowering effect (average of 2–3 mmHg) in adults with hypertension, but there is no evidence that it improves cardiovascular events.

Although vitamin C, coenzyme Q10, omega-3 fatty acids, and magnesium are used for lowering blood pressure, there is no clear evidence to support their use in the prevention or treatment of hypertension.

Sodium can be reduced to 2400 mg/day or less if the desired BP goal is not achieved.

Potassium intake can be increased potassium intake to 4.7gm/day.

Physical activity: Engaging in aerobic physical activity for 3–4 sessions a week lasting on average of 40 min per session (moderate to vigorous intensity) or at least 150 min per week of moderate intensity is shown to be beneficial in reducing blood pressure.

Weight loss: The target body mass index is ≤25. Alternatively, a waist-to-height ratio < 0.5 is recommended.

Smoking cessation: Smoking cessation lowers blood pressure and heart rate, reducing overall cardiovascular morbidity and mortality.

Alcohol use: Limit to ≤2 alcoholic drinks per day for men and ≤1 alcoholic drink per day for women. One alcoholic drink is defined as 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits (10 g alcohol).

Other healthy drinks: Moderate consumption of coffee and green and black tea. Others include hibiscus tea, pomegranate juice, beetroot juice, and cocoa.

Relaxation techniques: There is sporadic evidence for yoga, transcendental meditation, acupuncture, and biofeedback techniques in lowering blood pressure.

Pharmacological Interventions

Pharmacological agents, in addition to lifestyle management, provide the primary basis for treatment of high blood pressure (Fig. 16.1). Based on the recent guidelines [7], pharmacotherapy should be initiated for persons with stage 1

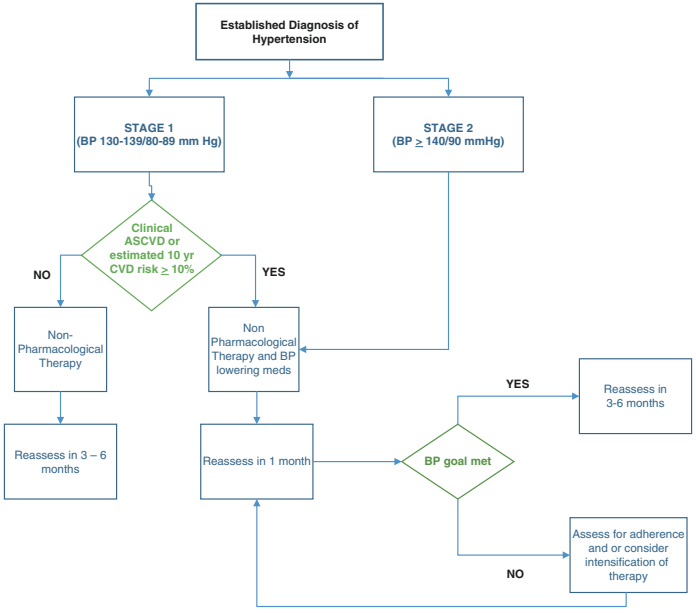

FIGURE 16.1 Algorithm for blood pressure thresholds, treatment recommendation and reassessments

hypertension with ASCVD or 10-year CVD risk ≥10% and stage 2 hypertension as mentioned in Table 16.3.

Current evidence demonstrates that antihypertensive pharmacotherapy not only lowers blood pressure but reduces the risk of cardiovascular disease, cerebrovascular events, and death [4]. Various classes of antihypertensive agents are available to treat high blood pressure. The primary agents used in the treatment of hypertension include thiazide diuretics, ACE Inhibitors, ARBs, and CCBs (Table 16.4). Drug combinations that have similar mechanisms of action or clinical effects

Table 16.3 AHA/ACC (2020) guideline recommendations by blood pressure category

BP category	Pressure ranges (mmHg)	Recommendations
Normal BP	<120/<80	Promote healthy lifestyle; reassess BP annually
Elevated BP	120–129/<80	Start with non-pharmacologic therapy; reassess BP in 3–6 months
Stage 1 hypertension	130–139/80–89	*ASCVD or 10-year CVD risk ≥10%* Start with both non-pharmacologic and pharmacologic therapy. Reassess BP in 1 month. If at goal, reassess every 3–6 months. If not at goal, assess for adherence and consider intensification of therapy *No ASCVD and 10-year CVD risk < 10%* Start with non-pharmacologic therapy; reassess BP in 3–6 months. If not at goal, consider initiation of pharmacologic therapy
Stage 2 hypertension	≥140/≥90	Start with both non-pharmacologic and pharmacologic therapy. Reassess BP in 1 month. If at goal, reassess every 3–6 months. If not at goal, assess for adherence and consider intensification of therapy

Table 16.4 Choice and indications of antihypertensive medications

Initial drugs of choice for hypertension	**Beta-1 selective beta-blockers (BB)** Safer in patients with COPD, asthma, diabetes, and peripheral vascular disease
• ACE inhibitor (ACEI) • Angiotensin receptor blocker (ARB) • Thiazide diuretic • Calcium channel blocker (CCB)	• Metoprolol • Bisoprolol • Betaxolol • Atenolol

Recommended indications

Indication	**Treatment choice**
Heart failure	ACEI/ ARB + BB + diuretic + spironolactone
Post-MI/clinical CAD	ACEI/ARB and BB
CAD	ACEI, BB, diuretic, CCB
Diabetes	ACEI/ARB, CCB, diuretic
CKD	ACEI/ARB
Recurrent stroke prevention	ACEI, diuretic
Pregnancy	Labetalol (first line), nifedipine, methyldopa

Source: Modified with permission from a card developed by Cole Glenn, Pharm D and James Taylor, Pharm D. www.nmhs.net/documents/27**JNC8**HTNGuidelinesBookBooklet.pdf [10]

should be avoided. Many patients started on a single pharmacological agent will subsequently require more than two drugs from different pharmacological classes to control blood pressure (Table 16.5). Initiation of antihypertensive drug therapy with a single drug is reasonable with stage 1 hyper-

Table 16.5 Summary of oral antihypertensive drugs

Class	Choice of medications	Comments
Diuretics	HCTZ 12.5–50 mg Chlorthalidone 12.5–25 mg Indapamide 1.25–2.5 mg Spironolactone 25–50 mg Eplerenone 50–100 mg Amiloride 5–10 mg Triamterene 100 mg Furosemide 20–80 mg Torsemide 10–40 mg Metolazone 2.5–5 mg Bumetanide 0.5–2 mg	Monitor for hypokalemia Most side effects are metabolic in nature Most effective when combined w/ACEI Stronger clinical evidence with chlorthalidone Spironolactone-gynecomastia and hyperkalemia Loop diuretics may be needed when GFR < 40 mL/min
ACEI/ARB	*ACEI* Lisinopril 10–40 mg Benazepril 10–40 mg Fosinopril 10–40 mg Quinapril 10–40 mg Ramipril 5–10 mg Trandolapril 2–8 mg Perindopril 4–16 mg *ARB* Candesartan 8–32 mg Valsartan 80–320 mg Losartan 50–100 mg Olmesartan 20–40 mg Telmisartan 20–80 mg Azilsartan 40–80 mg Eprosartan 600–800 mg	Side effects: Cough (ACEI only), angioedema (more with ACEI), hyperkalemia Losartan lowers uric acid levels; candesartan may prevent migraine headaches

(continued)

Table 16.5 (continued)

Class	Choice of medications	Comments
Beta-blockers	Atenolol 25–100 mg Betaxolol 5–20 mg Nadolol 40–120 mg Acebutolol 200–800 mg Penbutolol 10–40 mg Pindolol 10–60 mg Labetalol 200–800 mg Metoprolol succinate 50–100 mg and tartrate 50–100 mg, twice daily Nebivolol 5–10 mg Propranolol 40–120 mg twice daily carvedilol 6.25–25 mg twice daily Bisoprolol 5–10 mg Labetalol 100–300 mg twice daily	Not first-line agents; reserve for post-MI/CHF Cause fatigue and decreased heart rate Adversely affect glucose, mask hypoglycemic awareness
Calcium channel blockers	*Dihydropyridines* Amlodipine 5–10 mg Nifedipine ER 30–90 mg Nicardipine SR 60–120 mg Isradipine 5–10 mg Nisoldipine 17–34 mg Felodipine 2.5–10 mg *Non-dihydropyridine* Diltiazem ER 180–360 mg Verapamil 80–120 mg three times daily or ER 240–480 mg	Cause edema; dihydropyridines may be safely combined w/B--blocker Non-dihydropyridines reduce heart rate and proteinuria

Table 16.5 (continued)

Class	Choice of medications	Comments
Direct vasodilators	Hydralazine 25–100 mg twice daily, Minoxidil 5–10 mg	Hydralazine and minoxidil may cause reflex tachycardia and fluid detention–usually require diuretic + BB
Alpha-1 blockers	Terazosin 1–20 mg Doxazosin 1–16 mg Prazosin 2–20 mg	Alpha-blockers may cause orthostatic hypotension
Centrally-acting agents	Clonidine 0.1–0.2 mg twice daily methyldopa 250–500 mg twice daily Guanfacine 0.5–2 mg	Clonidine available in weekly patch formulation for resistant hypertension
Direct renin inhibitors	Aliskiren 150–300 mg	Very long acting, do not use with ACEI or ARB Avoid in pregnancy and CKD

tension with dosage titration and sequential addition of other agents to achieve the BP target. Initiation of antihypertensive drug therapy with two first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended with stage 2 hypertension and an average BP more than 20/10 mmHg above their BP target.

Various substances, including prescriptions medications, over-the-counter medications, illicit drugs, herbals, and food substances, may affect BP [4]. In the clinical assessment of hypertension, a careful history should be taken with regard to medications and substances (Table 16.6) that impair BP control. When feasible, any medications or substances associated with increased BP should be reduced or discontinued, and an alternative agent(s) should be used [4].

Table 16.6 Medications and substances that may cause high BP

Alcohol	Herbals (Ma Huang, St. John's Wort)
Amphetamines	Immunosuppressant (cyclosporine)
Antidepressants (MAOI, SNRIs)	Oral contraceptives
Atypical antipsychotics (clozapine, olanzapine)	Angiogenesis inhibitor (bevacizumab) and tyrosine kinase inhibitors (sunitinib)
Caffeine	Systemic corticosteroids
Decongestants (pseudoephedrine)	Recreational drugs (Cocaine, bath salts)

Office, Home Blood Pressure Monitoring (HBPM), and Ambulatory Blood Pressure Monitoring (ABPM)

Outpatient office measurements continue to be the most common means of diagnosing hypertension. The home and ambulatory readings are more consistent and better reflect hypertension-mediated organ damage (HMOD) risk and better differentiate white coat hypertension with elevated office measurements and masked hypertension, where measurements are lower in the office.

The office blood pressure measurement can vary by 20–25 mmHg between visits due to various factors and limitations such as poor technique, masked effect, white coat effect, and a small number of readings. Moreover, the traditional office blood pressure (BP) may not provide accurate estimates of blood pressure status. There are currently two methods of out of office blood pressure monitoring modalities that

Table 16.7 Blood pressure patterns that can be determined by office BP, ambulatory blood pressure monitoring ABPM and HBPM measurements

Blood pressure	Office BP	ABPM	HBPM
Predict events	+	+	+
Diagnostic utility	+	+	+
White coat hypertension	–	+	+/–
Masked hypertension	–	+	–
Measures diurnal variation of BP	–	+	–
Cost	Low	High	Low
Duration of drug effects	–	+	+
Reimbursement	Yes	Partial	No

have been recommended such as self or home monitoring (HBPM) and ambulatory blood pressure monitoring (Table 16.7). The blood pressure measured over 24 h by an ambulatory recording (ABPM) is the best method for estimating an individual's cardiovascular risk related to hypertension and response to antihypertension therapies [11]. The ABPM is also the most effective means to determine white coat or masked hypertension, and the BP values during sleep when nocturnal hypertension or non-dipping profiles are suspected (Fig. 16.2). For both self- and ambulatory blood pressure monitoring, the use of the upper arm is better than the wrist monitors, except in very obese individuals. Finger devices are not reliable. An up-to-date list of monitors can be retrieved from www.validatebp.org [12]. Currently, ABPM is being widely used in clinical practice, and the expenses are often reimbursed by most of the payors.

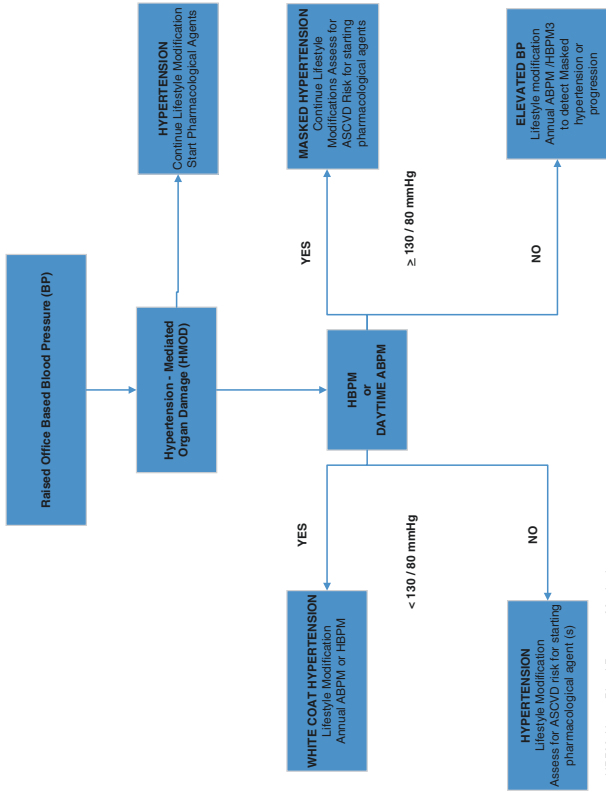

FIGURE 16.2 Algorithm and detection of elevated BP, masked, and white coat hypertension based on office BP, HBPM, and ABPM

Refractory or Resistant Hypertension

Refractory or resistant hypertension is defined as a blood pressure of at least 140/90 mmHg or at least 130/80 mmHg in patients with diabetes or renal disease (i.e., with a creatinine level of more than 1.5 mg/dL or urinary protein excretion of more than 300 mg over a 24-h period), despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic [13].

In order to diagnose refractory hypertension, various factors that needs to be considered are secondary causes of hypertension (Table 16.8), improper blood pressure measurement, volume overload, competing substances, obesity, nonadherence to treatment, inadequate doses or inappropriate combinations of medications, alcohol consumption, and other substances (Table 16.6).

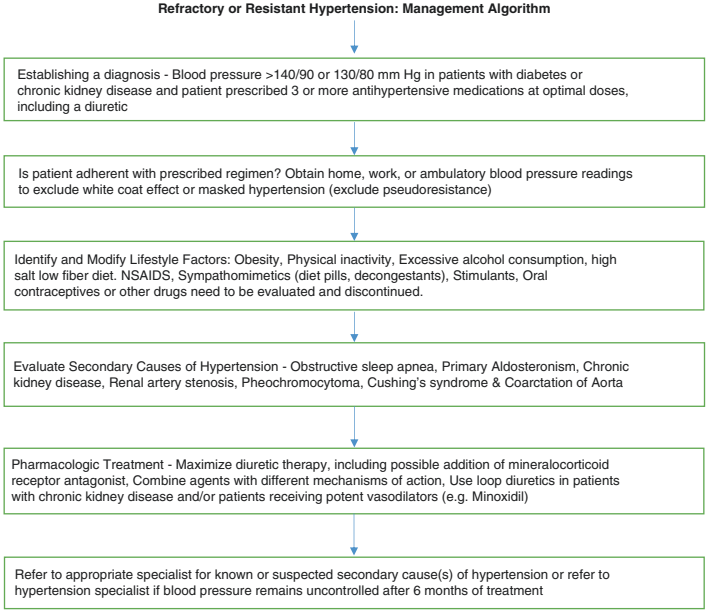

Table 16.8 Classification of hypertension in adults

Primary (essential benign or idiopathic)
Secondary
Renal
Parenchymal diseases
Vascular (renal artery stenosis)
Tumors (renin producing)
Adrenal
Cushing's disease
Primary aldosteronism
Pheochromocytoma
Endocrine
Hypothyroidism
Hyperthyroidism
Acromegaly
Carcinoid tumors
Vascular
Coarctation of aorta
Aortic regurgitation
Medications
Oral contraceptives
Erythropoietin
NSAIDS
Corticosteroids
Cyclosporine

Table 16.8 (continued)

Miscellaneous
Pregnancy
Perioperative period
Alcohol withdrawal
Obstructive sleep apnea
Caffeine
Nicotine

Role of Digital Health in Hypertension

Digital health innovations for hypertension include blood pressure sensors (cuffless monitors), smartphone-enabled upper arm blood pressure monitors, mobile applications, and remote monitoring technologies. Wearable trackers have the potential to improve hypertension control and medication adherence through real-time capture of clinical data, better connectivity with health care providers and medication reminder alerts. With increasing emphasis on home and ambulatory blood pressure monitoring to confirm hypertension prior to treatment, such devices also can help improve the diagnostic and treatment paradigm.

For wider adoption, device manufacturers and clinical researchers should collaborate on the development of clinical trials and evidence based guidelines for better clinical outcomes associated with emerging technologies.

Clinical Pearls

- Hypertension in its early stages is an asymptomatic process and has no clinical manifestations.
- Hypertension is preventable and an independent risk factor for end organ damage: myocardial infraction, stroke, heart failure, retinopathy, peripheral arterial disease, and end-stage renal disease (hypertension-mediated organ damage——HMOD).

- Social determinants and behavioral factors play an important role in the development of hypertension and its related complications.
- Lifestyle management including diet and physical activity are an integral part of blood pressure control along with pharmacological interventions.
- Adequate screening and control of blood pressure is an important clinical quality measure.

Don't Miss This!

- Hypertension can be either isolated systolic or diastolic or both systolic and diastolic.
- Secondary causes of hypertension should be assessed in patients with resistant hypertension.
- Ambulatory blood pressure monitoring (ABPM) is a useful tool in the management of hypertension.
- All antihypertensive medications have serious side effects especially ACE inhibitors, ARBs (angiotensin receptor blocker), and renin inhibitors that can cause fetal abnormalities and should be avoided in women of childbearing age.
- While prescribing pharmacological agents, one should consider associated medical illnesses and patient's preferences including cost of the medications.

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Chapter 17
Chest Pain

Adarsh Katamreddy

Chest Pain

Chest pain is a common clinical presentation encountered in the outpatient setting [1]. A systematic approach is required for timely diagnosis and management. The etiology for chest pain ranges from benign to potentially life-threatening causes [2]. Early identification of life-threatening causes and triaging to a higher level of care from an office setting is vital. In this chapter, we will review essential history, physical exam, and diagnosis strategies in the ambulatory setting. Chest pain is anxiety provoking in patients. Therefore, in addition to making the diagnosis, alleviating the patient's anxiety for benign causes of chest pain is essential.

History

Eliciting an accurate history is a crucial first step in making an accurate diagnosis. Using an open-ended style of questioning gives important clues about the underlying etiology. "Can

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you tell me more about the pain?" should be the first question. Then, teasing out further details regarding the onset, duration, precipitating factors, character, radiation, association with food, exertion, respiration, any history of similar pain, and the relation of pain to the movement of the upper extremities and neck are significant to note. After trying open-ended questioning, close-ended questions can be used to further clarify the diagnosis.

Past medical history of cardiovascular risk factors including diabetes, hypertension, hyperlipidemia, chronic inflammatory conditions, and surgical history of cardiac procedures increases the likelihood of coronary artery disease. In addition, smoking and cocaine use history and family history of cardiac disease should also be reviewed.

Physical Exam

Blood pressure, heart rate, temperature, and respiratory rate provide crucial diagnostic information. Jugular venous distention, examination of bilateral pulses, cardiopulmonary auscultation, and assessment of pedal edema are important. Inspection of the skin of the chest, palpation of the chest wall for tenderness, and active movements of the neck and both upper extremities should be performed based on the elicited history.

Differential Diagnosis

The causes can be broadly divided into:

1. Cardiac chest pain (Fig. 17.1)
2. Non-cardiac chest pain (Fig. 17.2)

The clinical features of various chest pain presentations are presented below.

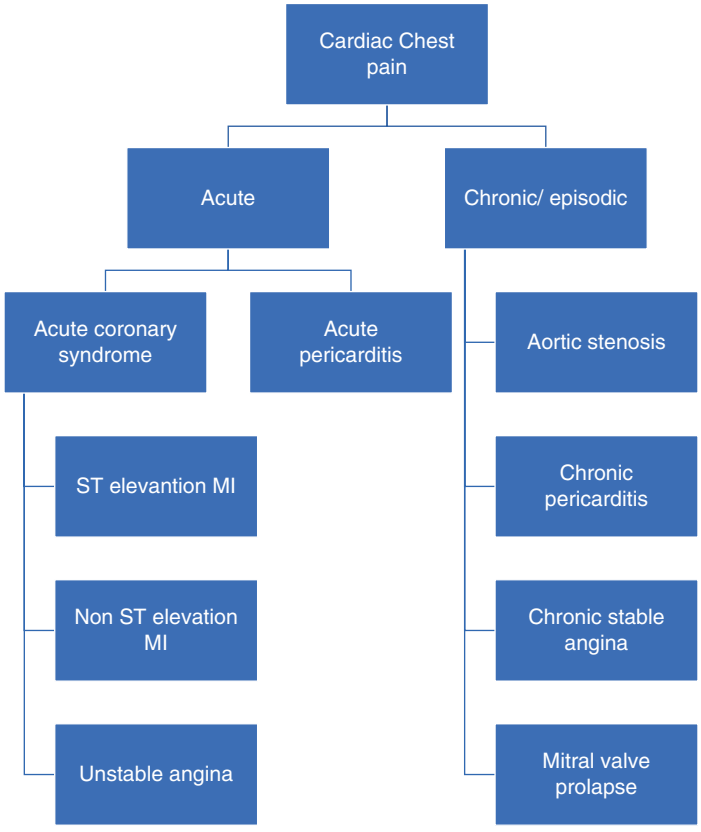

FIGURE 17.1 Cardiac chest pain causes

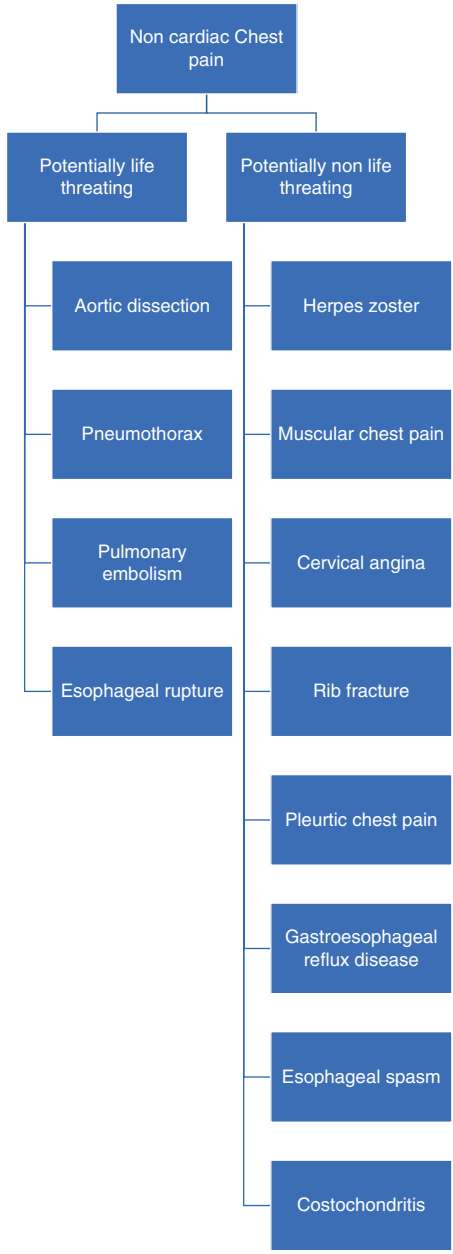

FIGURE 17.2 Non-cardiac chest pain causes

Potentially Life-Threatening

Patients presenting with any of the life-threatening causes should be managed emergently with an aim towards hemodynamic stability, and arrangements should be made to transfer to an emergency room swiftly under advanced cardiac life support staff supervision.

Acute Coronary Syndromes

Chest pain is substernal, dull, an sudden in onset, worsens over seconds to minutes, and worsens with exertion or emotional stress. Chest pain is often associated with shortness of breath and diaphoresis; radiates to the neck, jaw, right/left arm; and is sometimes present in the epigastric region. Chest pain improves with sublingual nitroglycerin (Table 17.1). The exam should pay particular focus on jugular venous distension, crackles on lung auscultation, pulses, and new murmurs.

Table 17.1 Clinical history for the diagnosis of acute myocardial infraction [8]

Pain descriptor	**Likelihood ratio (95% CI)**
Increased likelihood of AMI	
Radiation to right arm or shoulders	4.7 (1.9–12)
Radiation to both arms or shoulders	4.1 (2.5–6.5)
Associated with exertion	2.4 (1.5–3.8)
Radiation to left arm	2.3 (1.7–3.1)
Associated with diaphoresis	2.0 (1.9–2.2)
Associated with nausea and vomiting	1.9 (1.7–2.3)
Worse than previous angina or similar to previous MI	1.8 (1.6–2.0)
Described as pressure	1.3 (1.2–1.5)

(continued)

Table 17.1 (continued)

Pain descriptor	Likelihood ratio (95% CI)
Decreased likelihood of AMI	
Described as pleuritic	0.2 (0.1–0.3)
Described as positional	0.3 (0.2–0.5)
Described as sharp	0.3 (0.2–0.5)
Reproducible with palpation	0.3 (0.2–0.4)
Inframammary location	0.8 (0.7–0.9)
Not associated with exertion	0.8 (0.6–0.9)

Early identification of signs of cardiogenic dysfunction on the exam, including hypotension, tachycardia, elevated jugular venous pressure, and bilateral crackles, is essential. It is also important to note that acute coronary syndromes can present with pressure, tightness, or discomfort in the chest, shoulders, jaw, or upper extremities [3, 4].

Special populations: Women, patients with diabetes, and the elderly present with atypical symptoms more often. Some of the associated symptoms include shortness of breath, nausea or vomiting, lightheadedness, confusion, abdominal symptoms, syncope, or presyncope [3, 4].

Aortic Dissection

Aortic dissection is an often-missed diagnosis. Patients typically present with sudden, sharp pain radiating to the back. The presentation can be occult, and a high degree of suspicion is required. Palpation of peripheral pulses for symmetry and noting radio-radial and radio-femoral delays is essential. History of hypertension and elevated blood pressure on examination are important risk factors [5].

Pulmonary Embolism

Chest pain is acute in onset, worsens with respiration, and is associated with shortness of breath. Chest pain can be positional and is not consistently associated with exertion. History of prior deep vein thrombosis, prior pulmonary embolism, malignancy, family history of DVT, history of immobility, and fractures are important to note. Special attention should be placed on lower extremity examination; asymmetry, calf tenderness, and swelling should be noted on examination. Peripheral oxygen saturation should be assessed. Tachycardia and accentuated pulmonary component of the second heart sound (P2) may be heard on cardiac auscultation [6].

Pneumothorax

Patients present with sudden-onset chest pain, which is sharp, worsens with cough and deep inspiration, and is associated with shortness of breath. On exam, breath sounds are absent on the side of the pneumothorax. In addition, oxygen saturation, the position of the trachea, blood pressure, and variation with respiration should be noted [7]. Tension pneumothorax is associated with a shift of the trachea to the opposite side and pulsus paradoxus.

Primary pneumothorax is more common in young, tall males [7].

Non-Life-Threatening Causes

For the non-life-threatening causes of chest pain, a systematic approach to consider the various possible etiologies arising from the most superficial to the deepest anatomical structures will help avoid missing key etiologies. Etiologies involving the chest wall (skin, muscles, ribs, cartilage, nerves), pleura, pericardium, heart, trachea, and esophagus should be considered.

Some of the common non-life-threatening causes of chest pain are described below:

Gastroesophageal Reflux Disease

Patients with gastroesophageal reflux disease present with burning pain in the epigastric region with radiation to the chest and is usually associated with eating food and worsens with recumbency. Chest pain improves with antacid use and sitting upright [9]. Of note, inferior myocardial ischemia/infarction can occasionally present with epigastric pain and should be considered in all patients with sudden-onset epigastric pain [3].

Pleuritic Chest Pain

Pleuritic chest pain is sharp and localized and worsens with deep inspiration and cough. The pain is typically lateral to the midline. Patients can point to the site of pain with one finger. Pleuritic pain can be present with several conditions noted above, including pulmonary embolism, tension pneumothorax, and pericarditis. After evaluating the above etiologies, consideration should be given to pneumonia and viral pleurisy [10].

Cervical Angina

Cervical spondylosis is an often-missed cause of chest pain. Movement of the neck from side to side reproduces the pain. The pain is often described as sharp and radiates from the neck to the chest on the movement of the neck from side to side. Spurling's test should be performed if there is suspicion of cervical cause of chest pain [11].

Pericarditis

Chest pain is substernal and sharp, worsens with inspiration, gets better with sitting up, is not clearly associated with exertion, and often radiates to the right shoulder. On examination, a diastolic friction rub can be heard. Patients with a prior diagnosis of pericarditis often have the same characteristics of chest pain across episodes [12].

Chronic Angina

Chronic stable angina typically presents with substernal chest tightness, heaviness, or pain and is generally brought on by exertion and improves with nitroglycerin. Chest pain is often associated with shortness of breath. Typically, the characteristic of chest pain does not change across episodes [3]. Patients often have multiple cardiovascular risk factors. Examination of peripheral pulses is vital in these patients. Evidence of peripheral artery disease increases the risk of having coronary artery [13]. Patients with aortic stenosis can have exertional anginal symptoms late in the disease course. Presence of an ejection systolic murmur or absence of aortic component of second heart sound on auscultation are critical diagnostic clues that should prompt further evaluation [14].

Herpes Zoster

Patients present with vesicular rash in one or two dermatomes associated with burning pain. It is important to note that chest pain can precede the rash. Some patients have viral prodromal symptoms, including headache and malaise [15].

Muscular Pain

Muscular pain presents as a dull pain that is insidious in onset and positional and worsens with the movement of the arm and can be associated with localized tenderness. This pain is not associated with exertion.

Rib Fracture

Pain due to rib fractures worsens with deep breathing, and the patients typically take shallow breaths to avoid pain. History of trauma gives an important clue. Severe tenderness at the location of the fracture is observed. Metastatic malignancy to the rib should be considered in patients with known malignancy, with other histories suggestive of metastatic disease, including weight loss, poor appetite, and low energy.

Costochondritis

Chest pain due to costochondritis presents as anterior chest pain. Patients typically report worsening pain with movements of the upper extremities and deep breathing. Some patients have a history of severe exertional physical activity on the preceding days. Tenderness is present at the costochondral junctions on palpation [16].

Esophageal Spasm

Severe chest pain is associated with intake of food. In addition, patients report associated dysphagia and symptoms of gastroesophageal reflux disease. Chest pain due to esophageal spasms is also relieved by nitroglycerin, and there is no association with exertion.

Approach to Management in the Primary Care Setting

In the office setting, the approach to chest pain involves rapid evaluation based on history and physical exam for life-threatening causes and triaging to the appropriate level of care. Patients with non-life-threatening causes can be evaluated based on the possible etiology (Fig. 17.3).

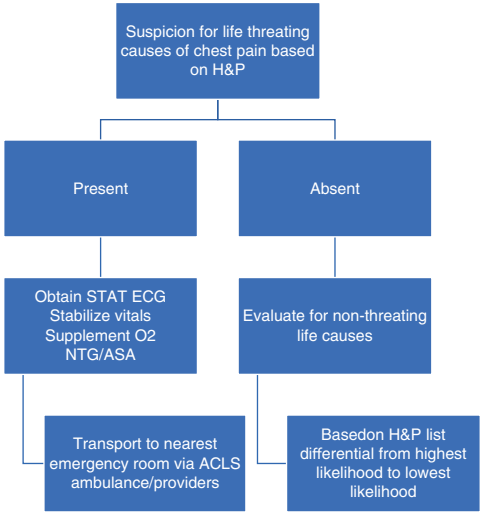

FIGURE 17.3 Approach to management in the primary care setting

Diagnostic Testing

Electrocardiogram

A 12-lead electrocardiogram is a simple, noninvasive diagnostic test that can be easily performed in the office setting and should be performed on most patients with cardiovascular risk factors unless suspicion for cardiac etiology is very low based on history and physical exam. The electrocardiogram should be compared to prior electrocardiograms to evaluate for any changes [3].

Blood Testing

Blood testing does not add additional diagnostic information for chest wall pain and gastroesophageal reflux disease. Serum troponin, natriuretic peptide, and creatinine should be ordered if cardiac etiology of chest pain is suspected. Complete blood count, blood urea nitrogen, and creatinine should be ordered for patients with high suspicion for community-acquired pneumonia, which helps calculate the CURB-65 score. CURB-65 gives 1 point each for confusion, BUN >19 mg/dL, respiratory rate ≥30/min, systolic BP <90 mmHg or diastolic BP ≤60 mmHg, or age ≥65. Patients with scores 0 and 1 can be discharged home to receive oral therapy [17].

Imaging

Chest X-Ray

The chest x-ray is a simple, noninvasive diagnostic test with minimal radiation exposure. It helps assess for pneumonia, cardiac silhouette, pulmonary vascular congestion, rib pathology, pneumothorax, and pleural effusion [3].

X-Ray C-Spine

For patients suspected of cervical angina, X-ray C-spine in AP and lateral views may show degenerative disease [11].

Transthoracic Echocardiogram

Patients with intermediate and high pretest probability for coronary artery disease and patients with suspicion for cardiac etiology of chest pain should undergo a transthoracic echocardiogram. Wall motion abnormalities, pericardiac effusion, systolic dysfunction, and valvular abnormalities can be detected. When point-of-care ultrasonography (POCUS) is

available and the providers have adequate experience, cardiac POCUS can help in further triaging patients with suspicion of acute coronary syndrome [3, 4, 12].

Diagnostic Testing for Obstructive Coronary Artery Disease

In the office setting, patients presenting with chronic stable angina should undergo further testing to evaluate for obstructive coronary artery disease, which is defined as ≥50% obstruction of any one of the epicardial coronary arteries. The approach to diagnostic testing is based on the pretest probability of coronary artery disease. Patients with low pretest probability do not need further testing. Patients with intermediate and high pretest probability need further testing. Patients with symptoms and high pretest probability should be given a cardiology referral to undergo invasive cardiac angiography.

In patients with intermediate pretest probability, the testing choice is based on local expertise, cost, and availability of testing [3]. Here, we briefly discuss the various testing modalities and discuss their use. Sensitivities and specificities of testing are noted in Table 17.2 [18].

Table 17.2 Sensitivity and specificity of diagnostic testing for obstructive coronary artery disease

Test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Exercise treadmill ECG test	58 (46–69)	62 (54–69)
Stress echocardiogram	85 (80–89)	82 (72–89)
CCTA	97 (93–99)	78 (67–86)
SPECT	87 (83–90)	70 (63–76)
PET	90 (78–96)	85 (78–90)
Stress CMR	90 (83–94)	80 (69–88)

In patients without baseline electrocardiographic abnormalities and ability to exercise ≥5 metabolic equivalents (METs) without limitations due to body habitus or underlying medical conditions such as osteoarthritis, peripheral artery disease, frailty, or severe pulmonary disease, exercise electrocardiography can be performed. Patients able to exercise to stage III on the Bruce protocol with a negative ECG have a low risk for CAD. Thus, exercise ECG provides important prognostic information [3].

CT coronary angiography (CCTA) is a noninvasive test that uses computed tomography to obtain high-resolution images of the coronary arteries. CCTA has higher sensitivity compared to stress imaging in detecting obstructive CAD. However, performing CCTA in patients with a BMI of more than 40 kg/m^2 is technically challenging. Stress testing can be achieved with stress echocardiography and stress SPECT/PET myocardial perfusion imaging (nuclear stress test). Stress testing can be performed with exercise or with pharmacologic agents. If the patient can exercise, exercise is preferred over pharmacologic agents as this provides additional prognostic information (Fig. 17.4). Patients undergoing CCTA vs. stress testing have similar outcomes at 2–3 years in randomized trials. If the choice of preferred testing modality is unclear, patients can be referred to cardiology [3].

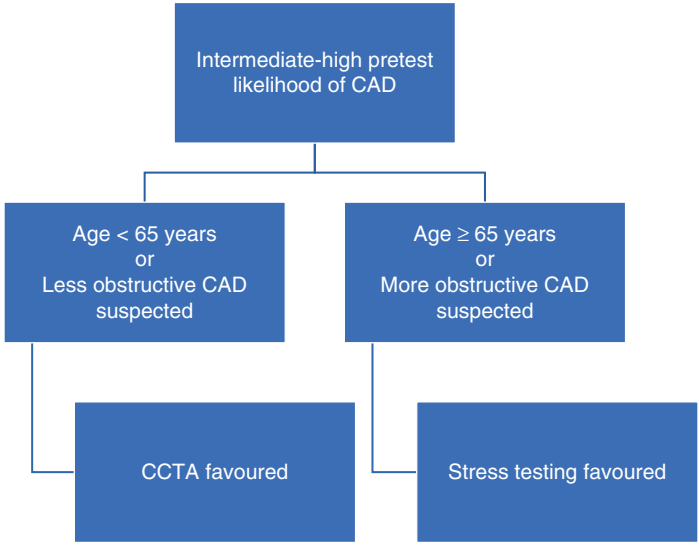

FIGURE 17.4 Approach to testing in intermediate–high pretest likelihood of coronary artery disease

Treatment of Non-Life-Threatening Causes of Chest Pain

Treatment is based on the underlying etiology.

Chest wall pain: Treatment of most causes of chest wall pain is conservative with pain control with acetaminophen or NSAIDs. Patients rarely need opioids to manage pain. Patients with herpes zoster symptom onset within 72 h or new skin lesions should receive antiviral therapy. Patients with cervical spondylosis benefit from physiotherapy to strengthen the muscles around the neck (Fig. 17.5a) [11, 15, 16].

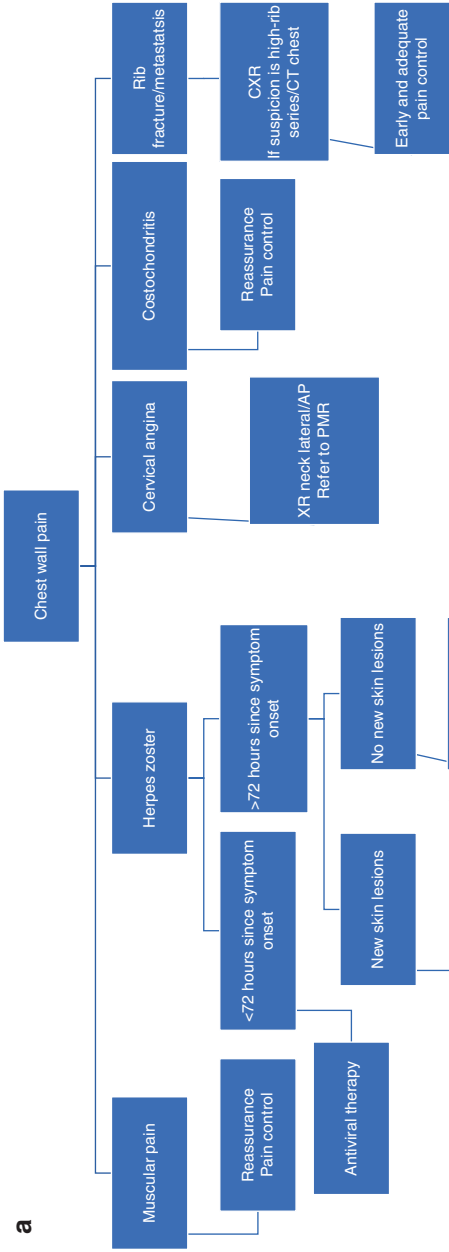

FIGURE 17.5 (**a**) Approach to chest wall pain, (**b**) Approach to gastroesophageal reflux disease, (**c**) Approach to pleuritic chest pain, (**d**) Approach to life-threatening cardiac causes of chest pain

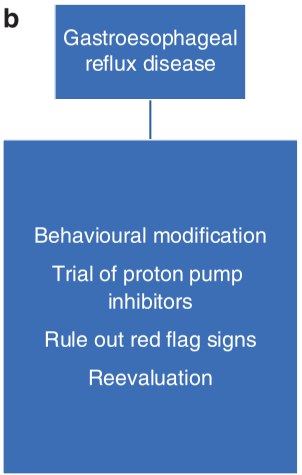

FIG.URE 17.5 (continued)

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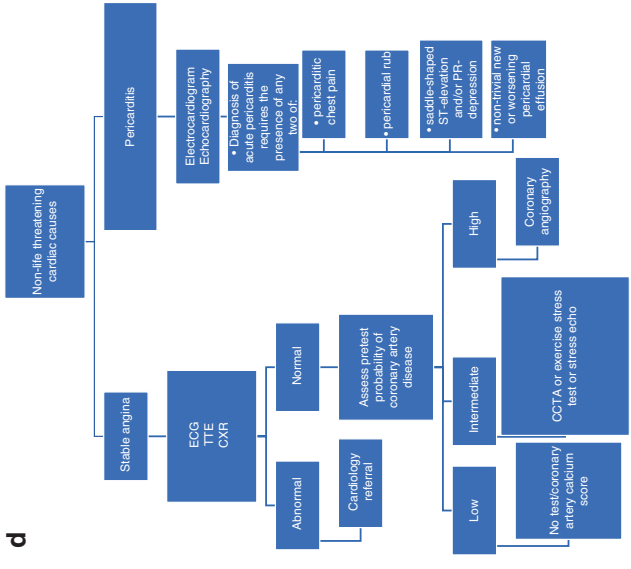

FIGURE 17.5 (continued)

Gastroesophageal reflux disease: Patients with typical features of gastroesophageal reflux disease should be evaluated for red flag signs such as dysphagia, odynophagia, GI bleeding, weight loss, and early satiety. A trial of proton pump inhibitors can be prescribed in the absence of red flags signs. Refer to gastroenterology if red flag signs are present or if esophageal dysmotility is suspected (Fig. 17.5b) [9].

Pneumonia: For patients presenting with community-acquired pneumonia, pneumonia severity based on CURB-65 or pneumonia severity index needs to be assessed. These prognostic tools will help decide if patients need inpatient admission for the management of community-acquired pneumonia [17]. CURB-65 score of 0 or 1 can be considered for treatment at home. Beta-lactams, alone or combined with macrolides, can be considered for empiric antibiotic coverage (Fig. 17.5c). Detailed discussion about the choice of antibiotics is available at the Infectious Disease Society of America (IDSA) guidelines [17].

Chronic stable angina: Patients with chronic stable angina should have 10-year atherosclerotic cardiovascular disease risk calculated, and cardiovascular risk factors such as diabetes and hypertension should be aggressively controlled. LDL cholesterol should be managed using statins. Nitrates are the cornerstone for symptom relief. Patients should be referred to cardiology if there is role for revascularization based on the diagnostic testing with CCTA or stress tests (Fig. 17.5d) [3].

Clinical Pearls

- A thorough history and physical examination are vital for an accurate diagnosis and management of patients presenting with chest pain.
- Having a broad differential diagnosis is essential for an accurate diagnosis of chest pain.
- Patients presenting with chest pain should be rapidly evaluated for life-threatening causes and triaged to the appropriate level of care.
- Cardiovascular risk factors should be evaluated in patients presenting with chest pain.

Don't Miss

- Inferior myocardial infarction can present as epigastric discomfort.
- Women, patients with diabetes, and elderly patients can present with atypical symptoms such as abdominal discomfort, fatigue, syncope, or presyncope in the setting of acute coronary syndrome.

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Chapter 18
Anemia

Benjamin Cohen

Introduction

Anemia is diagnosed when a patient's hemoglobin is less than 12 mg/dL in women and less than 13 mg/dL in men [1]. Alternatively, one can use the hematocrit to diagnose anemia. The typical ratio between RBC, hemoglobin, and hematocrit is 1:3:9. After determining the patient has anemia, we can look at the reticulocytes to calculate the reticulocyte index. The reticulocyte index adjusts the reticulocyte count based on the degree of anemia. A reticulocyte index >2% indicates hyperproliferation of erythrocytes and that the patient's anemia is from acute blood loss or hemolysis. A reticulocyte index <2% indicates that the anemia is due to hypoproliferation of erythrocytes. Additionally, the MCV will help us to further classify the cause of anemia into microcytic (<80 fL), normocytic (80–100 fL), and macrocytic (>100 fL) [2] (Fig. 18.1).

$$\text{Reticulocyte index} = \text{reticulocyte \%} \times \text{patient's hct} / 45 \div \text{maturation factor } [2]$$

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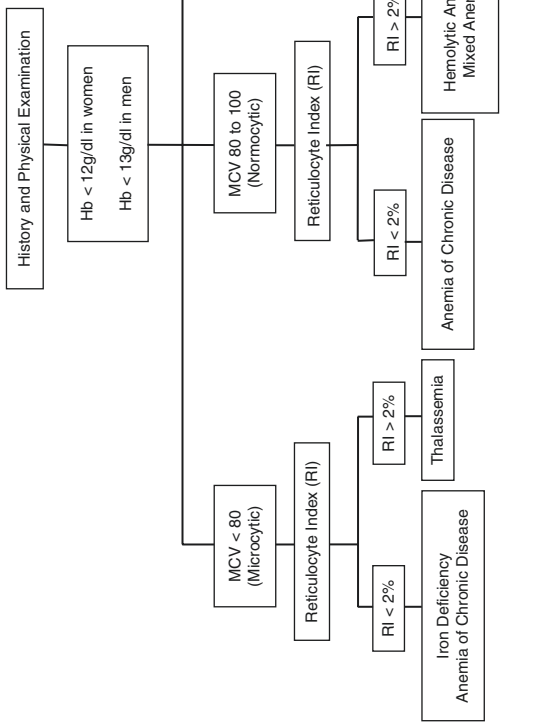

FIGURE 18.1 Anemia Algorithm

Hematocrit (%)	Maturation factor
≥35	1.0
25–35	1.5
20–25	2.0
<20	2.5

Key History and Physical Exam

The symptoms of anemia can often be vague and it is important to obtain a thorough history and physical exam to help identify the presence of this condition. When evaluating a patient for anemia, it is essential to identify underlying causes such as a history of bleeding, possibility of infection or malignancy, a history of autoimmune diseases, and adverse medication side effects. Determining the patients cultural and ethnic background along with a detailed family history may cue you into genetic disorders that cause anemia or perhaps a nutritional deficiency. Some common symptoms include fatigue, dizziness, palpitations, lightheadedness, dyspnea, and decreased exercise tolerance. A careful review of systems may also help lead to identifying the underlying cause of the patient's anemia. When assessing the physical exam, it is important to look for the presence of tachycardia or hypotension, as these could be some signs of severe anemia. In addition, the presence of pallor, glossitis, jaundice, and splenomegaly may be some physical exam findings to help with the diagnosis. It is important to note that symptoms may vary depending on the severity and speed at which a patient's anemia progresses. The reason for this is as erythrocytes become fewer in number, there is decreased oxygen delivery to essential tissue and organs [2]. For example, if a patient has an acute blood loss and a hemoglobin of 8 mg/dL, they may have some symptoms such as tachycardia or hypotension, whereas a patient with a chronic anemia from renal disease who also has a hemoglobin of 8 may only have fatigue.

Laboratory Evaluation

While history and physical exam can lead the provider towards a diagnosis and etiology of anemia, certain laboratory evaluation must be done to complete the evaluation:

- *Complete blood count (CBC)*: The first lab test that should be completed is the CBC. A CBC will reveal the red blood count (RBC), hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW). It will also reveal the platelet and white blood cell (WBC) count and differential, which may be high or low in certain types of anemias. It is important to know if the patient has isolated anemia or if there is the presence of other cytopenias.
- *Reticulocyte count*: Reticulocytes are immature red blood cells and can either be increased or decreased depending on the etiology of anemia. This will help to determine if the patient's anemia is due to hypoproliferation or increased destruction of erythrocytes.
- *Peripheral smear*: Obtaining a peripheral smear will show if there are certain characteristics of the red blood cell morphology that may help lead to a diagnosis (e.g., bite cells in G6PD deficiency) or even identify infections such as malaria or babesia.
- *Nutrients*: Iron, total iron binding capacity (TIBC), TIBC %, ferritin, B12, and folic acid.
- *Hemolysis*: Lactate dehydrogenase (LDH) haptoglobin, and indirect bilirubin.
- Sometimes more advanced evaluation needs to be completed and depending on the suspected etiology may include hemoglobin electrophoresis or bone marrow biopsy and analysis.

Hypoproliferative Anemias

These types of anemias are among the most common anemias and can be further classified based on whether they are microcytic, normocytic, or macrocytic [3].

Microcytic Anemia

Microcytic anemia is characterized by RBCs that are small in size with an MCV <80% [2]. The small size of the RBC is due to a decrease or deficiency in hemoglobin production. The causes of microcytic anemia include iron deficiency, inborn errors of the globin protein production, restriction of iron delivery to the heme group, and defects in the synthesis of the heme group.

Differential Diagnosis

- Iron deficiency anemia
- Thalassemia
- Anemia of chronic disease/inflammation
- Sideroblastic anemia

Iron Deficiency Anemia

Epidemiology

Iron deficiency anemia is the most common type of microcytic anemia and most common form of anemia in general, estimated to cause about 50% of all types of anemia. Iron deficiency anemia has a prevalence of 1–2% in the general population. Iron deficiency may be present without anemia in roughly 11% of the adult population [4].

Pathophysiology

Iron is an essential component in the creation of hemoglobin, the protein that binds oxygen in the blood. Without this essential component, the body is not able to undergo erythropoiesis [5]. This results in the formation of smaller RBCs.

The most common way to develop iron deficiency is through blood loss. In women, iron deficiency anemia is especially common due to menstrual bleeding. In addition, occult bleeding from a gastrointestinal source is common and can be a sign of malignancy such as colorectal cancer [3]. Since our RBCs contain a large percentage of the body's iron stores, when a patient has blood loss, iron stores are depleted more rapidly [5]. The remaining iron is stored in other iron-containing proteins (e.g., myoglobin, ferritin) or stored as hemosiderin.

Iron deficiency can rarely be caused by poor oral intake of iron-containing foods. The foods highest in iron include red meats, poultry, fish, green leafy vegetables, lentils, beans, and peas.

Aside from poor dietary intake, patient's with malabsorptive disorders may also develop iron deficiency. Iron is primarily absorbed in the duodenum and proximal jejunum [5]. Surgical resection of this area of the gastrointestinal tract or malabsorptive diseases such as Crohn's disease or celiac disease can also lead to insufficient absorption of dietary iron despite diets rich in iron. In certain endemic areas, malabsorptive disorders may also occur due to helminthic infections.

Finally, iron deficiency anemia may be secondary to increased iron requirements. In young children this is especially common since iron is an essential nutrition for growth and development. In the adult population, this is less common but occurs during pregnancy and during lactation.

Key History

Some additional features unique to iron deficiency anemia are as follows:

- Pica [3]—this is an abnormal craving of items that are non-food substances such as clay, starch, and chalk. One form

of pica that is common is known as pagophagia, which is a craving and repeated ingestion of ice.
- Restless leg syndrome [3]—This is a condition characterized by significant discomfort of the lower extremities that is relieved with movement. The cause of this is unclear, but may be due to depleted iron stores in the central nervous system.
- Beeturia [3]—this is the reddish discoloration of urine in patients with iron deficiency who ingest beets. This occurs in up to 80% of patients with iron deficiency anemia and is related to increased intestinal absorption of betanin (red pigmentation of beets), which is normally decolorized by ferric ions. This also may occur in up to 10–14% of patients without iron deficiency.
- Brittle integument [3].

Physical Exam

Some unique physical exam findings in iron deficiency anemia include evidence of bleeding such as bright red blood or ecchymosis, as well as signs of cheilosis, koilonychia, and glossitis [5].

Laboratory Evaluation

The laboratory evaluation is essential for the diagnosis of iron deficiency anemia and includes the following:

- CBC: hemoglobin, RDW, MCV, MCHC.
- Iron studies: ferritin, TIBC, TIBC%, and serum iron.
- Reticulocyte index should show a hypoproliferative anemia.
- Peripheral smear: hypochromic RBCs, microcytosis, and poikilocytosis.
- While no longer routinely done, bone marrow stained with Prussian blue can detect if there is absence of iron stores and help confirm the diagnosis.

Diagnosis

The diagnosis of iron deficiency is determined primarily through the laboratory evaluation listed above. The results of the lab evaluation should show a low serum iron concentration, low TIBC%, low ferritin, and high TIBC. In other words, iron concentration needs to be low and the TIBC, or total iron binding capacity, is high (there is a lot of room to bind iron), while the percentage of iron bound (TIBC%) is low (due to low serum iron concentration). The most sensitive test for the diagnosis of iron deficiency anemia is the ferritin, the major protein that binds iron. When ferritin levels drop below 15 μg/L, along with low serum iron concentration, it is diagnostic of iron deficiency [5]. In addition, a low ferritin will help distinguish iron deficiency from anemia of chronic disease. In anemia of chronic disease, ferritin, an acute phase reactant, is elevated and may confound our ability to determine if a patient has iron deficiency. When ferritin is greater than 100 ng/mL, iron deficiency is less likely.

Treatment

Understanding the etiology of iron deficiency is essential when choosing the right treatment options. In cases of asymptomatic iron deficiency, patients may be able to be treated by increasing their dietary intake of iron, if the deficiency is minimal. In a majority of cases it is reasonable to prescribe oral iron salts as appropriate iron supplementation. The most common and least expensive option is ferrous sulfate 325 mg. Each tablet contains 65 mg of elemental iron. Since only 10–20% of each iron tablet is absorbed, oral iron supplementation frequently causes gastrointestinal complaints such as nausea, bloating, abdominal cramps, and constipation. The color of the patient's stool may also turn to a black or grey color and must be distinguished from melena.

When providing oral iron supplementation, it is important to identify any antacids or fiber supplementations taken by the patient, as these medications may further impair iron absorption. Furthermore, taking oral iron supplements 2–3

times per day upregulates hepcidin, a protein that decreases iron absorption. Therefore, it is recommended to take oral iron supplementation only once per day, and if a patient has significant gastrointestinal side effects, this can be further decreased to every other day. The response to appropriate iron supplementation may be seen as quickly as after 1 week. Oral iron replacement should show normalization of iron levels and improvement in the anemia after 3–6 months of treatment [3].

When patients do not respond to oral iron supplementation, one must consider that the patient has either a malabsorptive disorder or that oral supplementation is not able to keep up with the rate of iron loss. In these patients it may be necessary to give them intravenous iron infusions. Intravenous iron infusions may improve reliability of iron absorption but does not improve the anemia more quickly than in patients taking oral supplementations. In addition, intravenous iron infusions carry the additional risk of anaphylaxis (particularly with iron dextran) [3, 5].

Finally, in patients with symptomatic anemia, acute anemia, or very low hemoglobin (<7 g/dL), it may be necessary to transfuse pRBCs.

Normocytic Anemia

This anemia is defined by those with an MCV between 80 and 100 [2]. This is typically more challenging to evaluate and there are multiple causes. Many anemias in their early stage present as normocytic anemia but then may later on show microcytosis or macrocytosis.

Differential Diagnosis [6]

- Early-stage nutritional deficiencies
- Hemolysis
- Anemia of chronic disease/inflammation
- Congestive heart failure

- Hypothyroidism
- Liver disease
- Alcohol use disorder
- Monoclonal gammopathies
- Early blood loss
- Partially treated anemia

Anemia of Chronic Disease/Inflammation (AOCD)

Epidemiology

AOCD is considered the second most common anemia behind iron deficiency anemia. It is estimated to effect anywhere between 33 and 60% of individuals with some source of chronic systemic inflammation such as rheumatoid arthritis [7]. Common causes of AOCD include infections, malignancy, and autoimmune disorders, advanced CKD, or end-stage kidney disease (ESKD). More recently, ACOD is considered as a cause for anemia in patients with severe trauma and diabetes.

Common infections associated with AOCD are HIV, osteomyelitis, tuberculosis, and endocarditis [7] due to their chronic or subacute nature.

Pathophysiology

AOCD is caused by a variety of disease states associated with systemic inflammation. As mentioned in the previous section, iron is an essential nutrient for many biological processes for humans, but it is also an essential nutrient for microbes. Therefore, it has been proposed that AOCD is an evolutionary mechanism to prevent iron from being accessible during times of infection or other types of chronic inflammation. This occurs via increased production of hepcidin in response to the inflammatory cytokines, including interleukin-6. As hepcidin increases, gut absorption of iron decreases. As hepcidin increases, more iron is kept stored in the reticuloendothelial system. This functional depletion in iron leads to decreased heme and then decreased erythrocyte production.

There is also a simultaneous decrease in erythropoietin (EPO), the hormone that stimulates erythrocyte production, and this process is also mediated by cytokines. Over time, with a decrease in EPO and a functional depletion of iron, patients often initially present with a normocytic anemia. However, as time progresses, if the underlying inflammatory cause is not corrected, it can lead to microcytic anemia [7].

Key History and Physical Exam

History taking and physical exam findings should focus on identifying the underlying cause for AOCD, whether that is an infection, malignancy, or rheumatologic condition.

Laboratory Evaluation

- CBC: normocytic or microcytic anemia.
- Iron, TIBC, TIBC%, ferritin.
- Reticulocyte count.
- Consider workup for malignancy, infection, or rheumatologic diseases based on your patient's history and physical exam findings: HIV, QuantiFERON, ESR, CRP, ANA, ANCA, colonoscopy, etc.

Diagnosis

The diagnosis of AOCD is based on the identification of a source of chronic inflammation as well as specific lab tests. The CBC may show normocytic anemia in early stages of the disease, but may progress to microcytic anemia later. Iron studies are particularly helpful in determining the diagnosis. In particular, these patients have high ferritin levels in conjunction with low TIBC and high TIBC%.

It is important to try and identify if, in addition to AOCD, there is iron deficiency. This may be suspected in patients with ferritin lower than expected and with more severe microcytosis. Laboratory interpretation may be difficult, but if the ratio of the TIBC%/log ferritin is less than 1, then this is suggestive of AOCD. If the ratio is greater than 2, it suggests combined iron deficiency anemia and AOCD [8].

Treatment

Treatment for AOCD is focused on treating the underlying cause of the inflammation. Blood transfusions are not typically recommended unless there is evidence of severe anemia. In patients with ESKD who do not make EPO, it is reasonable to consider EPO injections, although it is important to monitor for signs of hypertension and thrombosis if EPO analogs are used.

Macrocytic Anemia

These are the anemias defined as those with an MCV >100 [2]. This type of anemia is caused by abnormalities of RBC production in the bone marrow, or with altered RBC membrane compositions. The most common causes of macrocytic anemia are vitamin B12 and folic acid deficiency [9]. Other etiologies include myelodysplastic syndrome and alcohol-induced anemia. In patients with a reticulocytosis, a macrocytic anemia may also be identified. Reticulocytes are immature erythrocytes and are typically larger than the mature erythrocyte. Therefore, with reticulocytosis, the large number of immature erythrocytes inflates the MCV.

Differential Diagnosis [2]

- Vitamin B12 deficiency
- Folic acid deficiency
- Drug side effect
- Reticulocytosis
- Aplastic anemia
- Myelodysplastic syndrome
- Sideroblastic anemia
- Liver disease
- Alcohol use disorder
- Multiple myeloma
- Hypothyroidism

Megaloblastic Anemia

This is a macrocytic anemia that results from impaired DNA synthesis. The most common causes include the nutritional deficiencies of folic acid (B9) or cobalamin (B12) [9]. Additionally, there are many medications that can cause megaloblastic anemia through impaired absorption of either B12 or folic acid.

Vitamin B12 Deficiency

Epidemiology

There many causes for vitamin B12 deficiency. Since we cannot synthesize it on our own, it is important that we obtain it in our diet. This essential nutrient is found in animal products such as meats, seafood, dairy products, and eggs. Many foods such as cereals are also fortified with vitamin B12. It has therefore become very uncommon for people to develop vitamin B12 deficiency due to lack of dietary intake, especially in developed countries. The people at most risk include those who adhere to a strict vegan or vegetarian diet. The average person is able to store 2–3 mg of B12, and this is generally considered enough to maintain an individual for 3–4 years [9].

While developing vitamin B12 deficiency solely due to lack of dietary intake is rare, it is more common to develop the deficiency due to a malabsorptive process. Malabsorption can occur anywhere between the stomach and the terminal ileum, the location where it is ultimately absorbed before storing it in the liver. Common causes of malabsorption due to pathology in the stomach include pernicious anemia, atrophic gastritis, chronic H2 blockers or proton pump inhibitor use, and *Helicobacter pylori* infection. In the duodenum, pathologic causes for malabsorbtion include small intenstinal bacterial overgrowth and pancreatic insufficency. In the terminal ileum, malabsorption may be caused by ileal resection, ileitis such as in Chron's disease, chronic metformin use, and fish tapeworm infection from *Diphyllobothrium latum*.

Pathophysiology

As mentioned above, vitamin B12 deficiency may arise due to many causes but is mainly due to either poor nutritional intake, or more commonly due to a malabsorptive process. After we eat food and it passes through the stomach into the small intestine, B12 is bound by intrinsic factor, a protein that actively helps with absorption of B12 in the ileum. Alterations to gastric acid secretion from medications such as proton pump inhibitors and H2 blockers prevent B12 bound in food from being bound by intrinsic factor. In the terminal ileum, inflammation from Crohn's disease or infection from *D. latum* leads to poor absorption locally in the terminal ileum and can also lead to deficiency.

History and Physical Exam

Vitamin B12 deficiency may manifest with anemia, pancytopenia, jaundice, or neuropsychiatric symptoms, and therefore, a complete history and physical exam are essential when diagnosing and determining the severity of illness associated with B12 deficiency. Vitamin B12 plays a role in myelin basic protein, which is important to maintain the myelin that insulates peripheral nerves, and thus, deficiency can lead to neuropathy. The classic neurologic symptoms associated with vitamin B12 deficiency are known as subacute combined degeneration and occur due to demyelination of the dorsal and lateral column of the spinal cord. As the disease progresses, patients may experience weakness, ataxia, spasticity, and ultimately paraplegia. Other symptoms include depressed mood, irritability, dementia, cognitive slowing, visual disturbances from optic atrophy, abnormal deep tendon reflexes, and glossitis. The neuropsychiatric manifestations of vitamin B12 deficiency may occur without the presence of anemia, and the absence of anemia should not rule out this nutritional deficiency as a cause for any of the above neuropsychiatric symptoms [9].

Laboratory Evaluation

- CBC
- Peripheral smear—presence of macrocytes and hypersegmented neutrophils

- Intrinsic factor antibodies, parietal cell antibodies
- B12 and folic acid level
- Methylmalonic acid and homocysteine level
- Schilling test—no longer routinely done [3]

Diagnosis

In most cases, B12 levels should be checked when the CBC reveals a macrocytic anemia. For the majority of patients, we do not check folic acid levels, as a deficiency is very uncommon in patients with a routine diet in resource-rich areas and is only of benefit in patients with poor oral intake or frequent alcohol use [3]. The diagnosis of vitamin B12 deficiency can sometimes be obscure. The normal value of vitamin B12 is greater than 300 pg/mL, and when the level is higher than this, it is considered to be 90% sensitive to rule out B12 deficiency. When patients have values less than 200 pg/mL, that is sufficient to diagnose a B12 deficiency. The evaluation can become obscure when values range between 200 and 300 pg/mL. When this occurs, it is appropriate to assess for serum methylmalonic acid (MMA) and serum homocysteine levels, proteins that are intermediaries in the metabolism of vitamin B12. In scenarios where both MMA and homocysteine levels are normal, vitamin B12 deficiency is ruled out. Elevation in both the MMA and homocysteine levels confirms a diagnosis of vitamin B12 deficiency [10] (this would not rule out a simultaneous folic acid deficiency). If MMA is normal and homocysteine levels are elevated, this is more consistent with a folic acid deficiency.

When choosing a treatment option for B12 deficiency, it is important to identify the cause and severity of the deficiency and the anemia. The scenarios where correction is urgent include the patients with symptomatic anemia or Hb <8 g/dL, neuropsychiatric or neurologic symptoms, or in the presence of a malabsorptive process such as pernicious anemia. In these scenarios it is recommended to initiate treatment promptly with intramuscular cyanocobalamin. Treatment should consist of intramuscular injections 1–2 times per week for 2 weeks, followed by weekly injections until clinical improvement is seen, after which repeat CBC and reevaluation of symptoms

should be completed. If results show resolution of macrocytosis, anemia, and/or improvement in the neuropsychiatric or neurologic symptoms, the patient should continue with oral cyanocobalamin 1000 μg daily or monthly intramuscular injections indefinitely. In less severe cases, patients can be started on oral cyanocobalamin 1000 μg daily [10].

Folic Acid Deficiency

Folic acid deficiency is less common than vitamin B12 deficiency. Folic acid is an essential part of DNA synthesis, and so deficiency leads to megaloblastic anemia. It presents similarly to vitamin B12 deficiency, although the neuropsychiatric symptoms are less common, and it does not cause subacute combined degeneration. The most common cause for folate deficiency is due to medication side effects or alcohol use disorder. In resource-rich countries, many grains are enriched with folic acid, and therefore, it is very difficult to develop a deficiency due to poor intake [2]. In contrast with B12 deficiency, folic acid deficiency can develop quickly after about 3–4 months if a person is cut off from all sources of folate. Deficiency may also arise in the presence of rapid turnover of erythrocytes, such as in hemolytic anemia. Common medications that cause folic acid deficiency include methotrexate, trimethoprim, and phenytoin. Patients taking these medications should also be taking folic acid supplementation [10].

Diagnosis is made on lab testing demonstrating low folic acid levels. Peripheral smear will show similar findings to vitamin B12 deficiency, with macrocytosis and hypersegmented neutrophils. When the diagnosis is uncertain, MMA and homocysteine levels may be evaluated, and lab testing will show normal MMA and elevated homocysteine levels.

Treatment of folic acid deficiency, regardless of cause, is with supplementation of 1 mg of folic acid daily. Patients with alcohol use disorder should be counseled on strategies to decrease or cease their alcohol consumption [10]. In cases of severe deficiency due to medication side effect, the patient should have a discussion with their provider about whether or not to continue the medication or to pursue alternative therapies.

Hyperproliferative Anemia

This group of anemias is typically more complicated to treat. The causes include sickle cell diseases, hemolytic anemias, and rapid blood loss. In cases other than rapid blood loss, patients should be evaluated by a hematologist.

Hemolytic Anemia

In healthy individuals, an erythrocyte lives for about 90 days, during which about 1% of erythrocytes are destroyed per day. Hemolytic anemia is the process where there is premature destruction of erythrocytes. When erythrocytes are destroyed, the body responds with a reticulocytosis, increasing production of immature RBCs to help replace those that were destroyed. As the erythrocytes are destroyed, lactate dehydrogenase (LDH) is released. In addition, haptoglobin, a protein that binds free hemoglobin, decreases, as it is consumed. The remaining free hemoglobin is also metabolized into unconjugated bilirubin. Thus, the hallmarks of hemolytic anemia are elevated serum LDH and unconjugated bilirubin and decreased or undetectable serum haptoglobin.

Hemolytic anemias are classified as being either intrinsic or extrinsic [11].

Intrinsic Hemolytic Anemia

These are the hemolytic anemias that are caused by some acquired, inherited, or congenital hemoglobinopathy, RBC membrane defect, or enzyme deficiency [11]. Causes of intrinsic hemolytic anemia include the following:

- Hemoglobinopathy
  - Sickle cell anemia
  - Thalassemia
- RBC membrane defect
  - Hereditary spherocytosis
  - Hereditary elliptocytosis

- Enzyme deficiency
  - G6PD—glucose-6-phosphate deficiency

Sickle Cell Anemia

Epidemiology

Sickle cell anemia is the most common hemoglobinopathy. It is estimated to affect approximately 100,000 Americans each year. It is more prevalent in the African American community and estimated to occur in 1 out of 365 births. Approximately 1 in 13 births in the African American community has sickle cell trait. Finally, it is estimated to occur in 1 out of every 16,300 births in the Hispanic-American community [12]. It is theorized that sickle cell anemia is more common in areas with malaria, as it provided a selective benefit of protecting individuals from becoming infected with the parasite that causes malaria.

Pathophysiology

Sickle cell anemia (SCA) is an autosomal recessive disease, and so in order to have the disease, a person must inherit one copy of the defective gene from each parent [13]. In SCA there is a mutation in the beta-globin gene where the hydrophilic nucleotide glutamic acid is replaced with the hydrophobic nucleotide valine at the sixth position of the beta-globin gene, resulting in hemoglobin S (HbS). When the HbS is exposed to deoxygenated environments, polymerization of HbS occurs leading to erythrocyte rigidity and distortion of the erythrocyte membrane, creating the characteristic sickle shape. The rate at which this occurs depends on the concentration of HbS and hemoglobin F (HbF). This sickling leads to premature intravascular hemolysis, which causes vascular injury and endothelial dysfunction. The hemolytic process also depletes available nitric oxide, leading to vasoconstriction. This process also leads to release of inflammatory mediators and overexpression of adhesion molecules, leading to vaso-occlusion [14].

The main pathologies associated with sickle cell anemia are vaso-occlusive crisis, hemolysis, and certain infections [14]:

- *Hemolysis*: The baseline hemoglobin levels are often lower than the average adult due to the shorter life span of their erythrocytes. The rate of hemolysis may increase during times of increased stress such as during an infection, and the patient with SCA will be more prone to vaso-occlusive crisis. The most severe form of this is known as a hyperhemolytic crisis.
- *Vaso-occlusive crisis*: These episodes are often marked by severe pain and can lead to infarction at different locations in the body. The most severe complications of vaso-occlusive crisis include acute chest syndrome, acute papillary necrosis, both ischemic and hemorrhagic stroke, spinal cord infarction, cholecystitis, acute coronary syndrome, and pulmonary embolism. Patients with SCA often develop chronic lifelong pain that may be difficult to treat. Many of these patients may require opioid analgesia and it is important to carefully monitor these patients for signs of opioid addiction and withdrawal. Other complications include osteoporosis, avascular necrosis, pulmonary hypertension, and priapism.
- *Infection*: Patients with sickle cell anemia are at higher risk for osteomyelitis. Patients will develop splenic infarcts and are considered to have functional asplenia, putting them at higher risk for infections from encapsulated bacteria such as *Streptococcus pneumoniae, Neisseria meningitis,* and *Haemophilus influenzae* type B and gram-negative organisms such as *Salmonella* sp., *Enterobacter cloacae, Enterococcus faecium, and Pseudomonas aeruginosa.*

Key History and Physical Exam

For patients with SCA it is important to determine the severity of their illness. Each patient may present differently and with a different level of disease burden. History should focus on determining evidence of any complications due to SCA,

and given the widespread effects across all organ systems, it is important that a thorough review of systems is performed for each patient. It is important to determine whether a patient's pain is adequately controlled or not. Understanding what medications have been used and how often blood transfusions have been required may guide your treatment plan.

A full physical exam should be performed to evaluate for any neurologic deficits, conjunctival pallor, tachycardia, jaundice, gait abnormalities, and dactylitis.

Laboratory Evaluation

- CBC
- Hemoglobin electrophoresis
- Reticulocyte index
- LDH, haptoglobin, unconjugated bilirubin
- Peripheral blood smear

Diagnosis

Diagnosis of sickle cell anemia is based on RBC morphology on a peripheral blood smear along with clinical criteria of hemolysis with a history of ischemic pain. The diagnosis is confirmed with hemoglobin electrophoresis, which will show elevated levels of HbS.

Treatment

The overall management of sickle cell anemia varies depending on the severity of the illness and each patient should be managed with the help of a hematologist. For the severe complications such as acute chest syndrome, stroke, transient ischemic attack (TIA), spinal infarcts, hyperhemolytic crisis, and severe infections, or in cases where pain cannot be controlled at home, patients should be referred to their local hospital for further management.

For patients with less severe symptoms, outpatient management is recommended. All patients should be started on folic acid supplementation, as the sickled erythrocytes have a very short life span of 12–16 days and the folic acid is needed

for erythrocytosis and the rapid turnover of RBCs. Pain management should focus on use of NSAIDs for mild to moderate pain control [15].

Studies have found that patients with higher levels of fetal hemoglobin (HbF) have milder courses of disease and decreased hospitalization and may have improved survival [13]. In normal physiology, the fetus has high concentrations of HbF but after birth this gene is turned off and the gene for HbA, or in the case of patients with SCA, HbS, is turned on. The medication hydroxyurea, which is used as a chemotherapy agent by halting the cell cycle between G1 and S phases, also has the advantage of increasing HbF production and is recommended for all patients with sickle cell anemia who have had repeated complications from vaso-occlusive crisis or have had painful crisis more than three times per year [13].

In addition to hydroxyurea, it may sometimes be necessary to give a blood transfusion, particularly if a patient is having any of the more severe complications of a vaso-occlusive crisis.

All patients with sickle cell anemia should receive appropriate pneumococcal and HiB vaccinations to protect against these encapsulated organisms if they have not already received them earlier in life.

Thalassemia

Epidemiology

Thalassemia is another common hemoglobinopathy. It is estimated that roughly 20% of the world population carries a gene for alpha thalassemia, and 5.2% of the population has a significant form of the disease, either beta-thalassemia or alpha-thalassemia trait. Thalassemia is most prevalent in African and Mediterranean countries, the Middle East, and Southeast Asia. The most common form is the heterozygous form of disease. The homozygous alpha-thalassemia causes intrauterine demise and homozygous beta-thalassemia is associated with a severe anemia diagnosed at early age [16].

Pathophysiology

Thalassemia is a group of heterogenous hemoglobinopathies that results in decreased production of either the alpha or beta globin gene on the hemoglobin molecule. Hemoglobin is a tetramer that is composed of two alpha and two beta globin molecules. The beta globin molecule has two genes and the alpha globin gene has four genes. The spectrum of the different thalassemia disorders is dependent on how many genes are lost due to mutation. These mutations leads to a mismatch in the alpha/beta globin ratio, cellular damage, and early hemolysis [2].

Key History and Physical Exam

When evaluating for possible thalassemia disorders, it is important to obtain a complete social and family history. The patient's country of origin, or whether their parents have any hemoglobinopathy, can help you determine whether it is likely that a patient could have a thalassemia disorder. Since the laboratory evaluation will show microcytic anemia, it is important that your history and physical exam focus on ruling out causes for iron deficiency anemia.

Laboratory Evaluation

- CBC
- Iron studies
- Hemoglobin electrophoresis
- DNA sequencing
- Peripheral blood smear

Diagnosis and Management

The evaluation for thalassemia often begins when pursuing causes of microcytic anemia. Therefore, just like with iron deficiency anemia, the evaluation should begin with checking the CBC and iron studies. Patients with thalassemia will often have a mild anemia and a very low MCV. In contrast to iron deficiency anemia, the iron studies in these patients will not

be consistent with iron deficiency anemia. When evaluating the CBC, clinicians can use the Mentzer index to help determine the likelihood of thalassemia over iron deficiency. The Mentzer index is calculated by taking the MCV and dividing by the RBC count on the CBC. When this result is less than 13, it is suggestive of thalassemia.

After ruling out iron deficiency, a hemoglobin electrophoresis can be performed. This is helpful only in the diagnosis of beta-thalassemia disorders. Hemoglobin electrophoresis will show an increased production of HbA2 or HbF, and this is diagnostic of beta-thalassemia [15]. The diagnosis of alpha-thalassemia requires genetic testing to directly sequence the hemoglobin A gene for mutations. Additionally, the peripheral blood smear may show target cells, although this is not specific just to thalassemia [15].

Thalassemia disorders can be classified as follows [2]:

- Beta-thalassemia major: This occurs when both beta globin genes are missing. Patients typically are transfusion dependent. This is usually diagnosed early in childhood.
- Beta-thalassemia minor: This occurs when one of the beta globin genes is missing. Patients are often diagnosed when evaluating for causes of hypochromic and microcytic anemias. The anemia is mild and hemoglobin electrophoresis shows increased production of HbA2 or HbF.
- Alpha-thalassemia minima: This occurs when one out of four alpha globin genes is missing. These patients are asymptomatic. Genetic counseling is recommended if this disorder is identified.
- Alpha-thalassemia minor: This occurs when two out of four alpha globin genes are missing. Patients present similarly to beta-thalassemia minor, with mild and generally asymptomatic anemia. Diagnosis must be made through genetic sequencing of the alpha globin gene.
- Alpha-thalassemia intermedia: This occurs when three out of four alpha globin genes are missing. This typically presents during gestation and later with neonatal jaundice and a chronic hemolytic anemia. As patients reach the second

and third decade of life, patients may become transfusion dependent.
- Alpha-thalassemia major (hemoglobin Bart's disease): This occurs when four out of four alpha globin genes are missing. This causes hydrops fetalis and is often fatal within hours of birth.

For patients who are diagnosed with thalassemia, it is important for them to receive folic acid supplementation, since the turnover of erythrocytes is increased. Iron supplementation should be avoided in these patients [2, 15].

Hereditary Spherocytosis (HS)

Epidemiology

Hereditary spherocytosis is an autosomal dominant disorder and is the most common type of hemolytic anemia caused by a red cell membrane defect [17]. It is estimated to affect 1 in 5000 people and is more common in people of Northern European descent [11].

Pathophysiology

Hereditary spherocytosis is caused by a defect in genes responsible for the production of the genes ankyrin and spectrin, proteins that are responsible for the structural integrity of the cell membrane. This leads to increased fragility of the cell membrane and increased destruction of erythrocytes as they pass through the spleen.

Key History and Physical Exam

The most important part of the history is the family history. This is an autosomal dominant disease, and so in order for a patient to have hereditary spherocytosis, at least one of the parents must have it as well, although sporadic mutation is still possible. Due to the fragility of the red cell membrane and increased erythrocyte destruction, physical exam may reveal splenomegaly, jaundice, or other common symptoms of anemia.

Laboratory Evaluation

- CBC
- Reticulocyte count
- Unconjugated bilirubin
- Lactate dehydrogenase
- Peripheral blood smear
- Flow cytometry with eosin-5-maleimide binding test
- Osmotic fragility test—although flow cytometry is now preferred

Diagnosis and Management

Evaluation usually is started when the peripheral blood smear shows spherocytosis and evidence of hemolytic anemia. The CBC will show varying degrees of anemia and is notable for an elevated MCHC >34 and is one of the only disease states where this occurs [11]. The degree of anemia in each individual is variable depending on which genes are affected in this disease and the penetrance. If the disease is suspected, flow cytometry is the preferred test as this test is estimated to have 95% sensitivity and specificity. Classically, the osmotic fragility test was used, but given the success of flow cytometry has become less common for diagnosis [2].

The disease can be classified as based on severity as follows [18]:

- HS trait: normal hemoglobin, bilirubin, reticulocyte count.
- Mild HS is estimated to affect 20–30% of individuals with HS. These patients often have a hemoglobin between 11 and 15 g/dL, bilirubin between 1 and 2 mg/dL, and reticulocytosis of 3–6%.
- Moderate HS is the most common presentation of disease and is estimated to affect 60–75% of individuals with HS. Hemoglobin ranges between 8 and 12 g/dL and reticulocytosis >6% and bilirubin greater than 2 mg/dL.
- Severe HS is present in about 5% of cases and is associated with hemoglobin less than 8 g/dL, reticulocytosis >10%, and bilirubin greater than 3 mg/dL.

It is important to note that patients with moderate or mild HS may often present asymptomatically and with a compensated hemolytic anemia, but medications or infections that cause bone marrow suppression may lead to decompensation and severe anemia.

In scenarios where acute and severe hemolytic anemia occur, it may be necessary to consider splenectomy. These patients should receive adequate vaccinations to protect against encapsulated organisms including vaccination for *Neisseria meningitides, Haemophilus influenzae,* and *Streptococcus pneumoniae* if they had not already received them.

When managing these patients, it is important to note that just like with other types of chronic hemolytic anemias, they should be given folic acid supplementation due to the high turnover of their erythrocytes and increased folic acid requirements.

Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD Deficiency)

Epidemiology

G6PD deficiency is an X-linked disorder and is the most common enzyme deficiency in human erythrocytes. It is estimated to affect upwards of 400 million people worldwide. It is more common in men than in women and in people of African, Mediterranean, and Asian descent [19].

Pathophysiology

G6PD is an enzyme involved in the pentose phosphate shunt, a biochemical process that converts NADP to its reduced form of NADPH. The role of NADPH in the erythrocyte is to prevent damage to the cell from oxidative stress, by acting as a substrate to glutathione reductase, which converts hydrogen peroxide into water. In G6PD deficiency, the inability to prevent oxidative stress, in the setting of exposure to certain oxidants, initially leads to depletion of glutathione reductase,

which then leads to oxidation of the sulfhydryl group on the hemoglobin molecule, causing hemoglobin to become an insoluble mass that attaches to the red cell membrane, forming the classical Heinz bodies seen on peripheral smear [11]. Since the hemoglobin molecule is no longer free flowing in the cell cytoplasm, erythrocyte loses its shape and becomes the classical bite cells seen on peripheral smear.

Exposures that can lead to oxidative stress include certain medications, foods, or chemical exposures. Common medications that are not safe to use in G6PD deficiency include [11]:

- Dapsone
- Fluoroquinolones
- Nitrofurantoin
- Primaquine
- Rasburicase
- Sulfonylureas
- Sulfa drugs

Common foods and chemicals not considered safe include:

- Fava beans
- Henna compounds
- Naphthalene (mothballs, lavatory deodorants)

History Physical Exam

A patient who is being evaluated for G6PD deficiency should focus on possible exposures or triggers, family history of G6PD deficiency, and a social history determining the patient's ethnic background. Physical exam may reveal scleral icterus and jaundice, and during an acute hemolytic crisis, anemia may also be severe and signs of acute anemia may be present.

Laboratory Evaluation

- CBC
- Unconjugated bilirubin, LDH, haptoglobin
- Peripheral blood smear
- G6PD activity assay

Diagnosis and Management

It is important to identify when it is necessary to screen for GDPD deficiency. Evaluation is typically performed either after a patient had an unexplained hemolytic anemia after exposure to an oxidant, or prior to initiating medications that could cause oxidative injury in patients from the appropriate ethnic background. Laboratory evaluation is the key to diagnosis and begins with a CBC and lab tests used to evaluate for hemolysis. Peripheral smear may reveal bite cells and Heinz bodies. In order to confirm a diagnosis, a G6PD activity assay must be done, but it is important to note that during a hemolytic event, since those cells with low G6PD will hemolyze, the test will only show the activity of RBCs with normal G6PD activity, and thus, there is a high false-negative rate. Therefore, it is recommended to wait 3 months after the hemolytic event to adequately assess G6PD activity. In cases where it is important to quickly know whether a patient has G6PD deficiency, there is a quantitative assay that can be used [20].

Management of G6PD deficiency focuses on avoiding known oxidative triggers. If a hemolytic event occurs, the oxidant that triggered the event should be removed as quickly as possible. Patients should be given IV fluids for hydration, and depending on the severity of the anemia, they may need a blood transfusion.

Extrinsic Hemolytic Anemia

These types of hemolytic anemia are caused by factors external to the RBC that causes it to be damaged or hemolyze. The causes of extrinsic hemolytic anemia include:

- Autoimmune hemolytic anemia
- Hypersplenism
- Liver disease
- Thrombotic microangiopathies
- Infections: malaria, babesiosis, *Clostridium perfringens*
- Mechanical damage, e.g., through mechanical heart valves

Autoimmune Hemolytic Anemia

This group of anemias is due to pathologic autoantibodies that bind to and destroy erythrocytes. Depending on the thermal reactivity of the autoantibodies, the disease can be classified as either warm or cold agglutinin disease [11].

Warm Autoimmune Hemolytic Anemia (WAHA)

Epidemiology

WAHA is the most common type of autoimmune hemolytic anemia. It is estimated to affect approximately 1–3 per 100,000 people every year. It can occur at any age group and is more common in women than in men [21].

Pathophysiology

WAHA occurs when IgG autoantibodies bind to the red cell membrane and cause hemolysis and consumption by the spleen. In the majority of cases, the inciting trigger is unknown. Whereas most cases thus remain idiopathic in nature, there are some known causes for WAHA. These include [2, 11]:

- Autoimmune diseases: systemic lupus erythematosus and Sjogren's disease
- Malignancies such as CLL
- HIV

History and Physical Exam

History should focus on identifying any known triggers for hemolytic anemia either from autoimmune disease or from recent infection. Determining if there is the possibility of a previously undiagnosed autoimmune disease is important.

Physical exam should look for signs of autoimmune diseases such as polyarthritis and synovitis, rashes, and lymphadenopathy. An assessment for hepatomegaly or splenomegaly can also help identify a cause.

Laboratory Evaluation

- CBC
- Unconjugated bilirubin, haptoglobin, LDH
- Peripheral Smear may show spherocytosis
- Direct Coombs test
- HIV test
- C3, C4, ANA, SSA ab, SSB ab, DSdna ab, and other appropriate antibodies if rheumatologic cause is being suspected or evaluated

Diagnosis and Management

Patients who show evidence of hemolysis, as part of their workup, should undergo testing for WAHA. Diagnosis of WAHA is confirmed with a positive direct Coombs test, a test that is able to detect the presence of antibodies attached to the RBC cell membrane. The direct Coombs test is considered to be 95% sensitive [2].

Treatment of WAHA should be performed with the aid of a hematologist. It focuses on immunosuppression with glucocorticoids or biologic agents such as rituximab. It is important to identify the need for blood transfusion, but during an acute hemolytic event, the transfusion may be consumed as well due to circulating IgG autoantibodies. In refractory cases, a splenectomy may be necessary. This would not eradicate the autoantibodies, but rather the location where the tagged erythrocytes are typically destroyed. If a patient required a splenectomy, appropriate vaccination against encapsulated organisms should be administered to the patient [2, 11].

Cold Autoimmune Hemolytic Anemia

Epidemiology

Cold autoimmune hemolytic anemia, also referred to as cold agglutinin disease (CAD), is less common than WAHA and is seen more often in elderly, compared to young patients [22].

Pathophysiology

CAD causes hemolytic anemia and is caused primarily by IgM autoantibodies which fixes complement and leads to complement-mediated intravascular hemolysis. These cases of anemia are typically milder than in WAHA [22].

Just like with WAHA, the majority of cases are idiopathic but some secondary causes are known. These include:

- Lymphoma
- Infections such as *Mycoplasma pneumoniae*, EBV, and CMV
- Waldenström's macroglobulinemia

History and Physical Exam

In patients with CAD, the most common presenting symptom is acrocyanosis, which is a dark grey or purplish discoloration of skin in the acral areas, namely, the fingertips, toes, nose, and ears [22]. History should focus on identifying symptoms of anemia and any possible secondary cause. Physical exam may identify acrocyanosis if something cold, such as ice, is applied to acral areas and evidence suggesting certain secondary causes such as lymphadenopathy in a patient with undiagnosed lymphoma.

Laboratory Assessment

- CBC
- Unconjugated bilirubin, haptoglobin, LDH
- Peripheral smear may show spherocytosis and also clumping of RBCs
- Direct Coombs test
- C3 DAT
- C3, C4
- Cold agglutinin titer
- Heterophile antibodies
- HIV test

Diagnosis and Management

Clinicians should be suspicious of CAD in elderly patients with unexplained chronic anemia or with complaints of acrocyanosis. When labs show evidence of hemolysis, a Coombs test can be performed. If the direct Coombs test is positive, then a more specific C3 direct antibody test should be performed. If this is also positive, a diagnosis of cold agglutinin disease is more likely, and a cold agglutinin titer may be assessed [22].

Management of cold agglutinin disease like with WAHA should be done with the aid of a hematologist. Unlike with WAHA, cold agglutinin disease is more difficult to treat. While patients may be able to reduce symptoms by avoiding cold weather, this is often difficult to achieve all the time. Therefore, glucocorticoids are often used next, but are effective in less than 15% of cases. Most patients will require treatment with biologic agents such as rituximab. Splenectomy has not been shown to be as effective as treating cold agglutinin disease, compared with WAHA, and is typically not performed unless it is determined that the cold agglutinin disease is caused by IgG (~3.5% of patients) [22].

Conclusion

Anemia is a condition that can manifest from many different causes. Being able to identify the symptoms and diagnosing the exact cause can be difficult, but by classifying the anemia appropriately, a clinician can help to narrow down the differential diagnosis and pursue the correct management.

Clinical Pearls

- Iron deficiency anemia in patients older than 50 years may indicate an underlying gastrointestinal malignancy such as colorectal cancer, and all patients should be evaluated through colonoscopy.
- Patients who do not respond to oral iron should be evaluated for malabsorptive disorders such as celiac disease.

- The Mentzer index may help hint towards an undiagnosed thalassemia when the MCV is very low.
- Patients diagnosed with pernicious anemia should be referred to a gastroenterologist for further evaluation and endoscopy given the higher risk of gastric cancer in these patients.
- All patients with sickle cell anemia or who have had a splenectomy should receive appropriate pneumococcal vaccinations to protect against encapsulated organisms, as these patients are particularly susceptible to severe infection.
- All patients with unexplained normocytic anemia should undergo evaluation for hemolytic anemia.

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Chapter 19
Edema

Valerie Jorge Cabrera

Introduction

Edema is defined as palpable swelling caused by accumulation of fluid in the interstitial space. Edema can be a localized phenomenon, or when generalized throughout the body, it is called anasarca. Different clinical conditions, including localized conditions (e.g., venous and lymphatic disease) and systemic conditions, such as cardiac, liver, and renal disease, can cause edema. The etiology of edema can usually be determined by a careful history and a physical examination. Routine labs can help rule out common conditions that cause edema.

The Starling forces are involved in maintaining the balance between the intravascular space and the interstitial space. Changes to this homeostasis can result in edema [1]. These physiologic forces include the gradient between the intravascular and extravascular hydrostatic pressures and the differences in oncotic pressure between the interstitial space and plasma. The hydrostatic pressure within the capillaries tends to drive fluid out of the capillaries, whereas the oncotic

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pressure exerted within the capillaries tends to draw fluid back. If the hydrostatic capillary pressure is increased or the capillary oncotic pressure is diminished, a condition favoring edema results. Conditions causing increased capillary permeability, those affecting the electrolyte balance of the body with sodium and chloride retention and decreased lymphatic drainage, can also lead to edema.

Differential Diagnosis

Peripheral edema is a nonspecific finding common to a host of diseases [2, 3]. The acute edema of a single limb (usually defined as occurring for less than 72 h) should raise suspicion for deep vein thrombosis (DVT), cellulitis, or a ruptured popliteal cyst (Fig. 19.1). In those patients with history of recent trauma or surgery, compartment syndrome should be considered. Complex regional pain syndrome, an entity that can occur weeks after limb trauma, manifests with pain, edema, and changes in skin color and temperature.

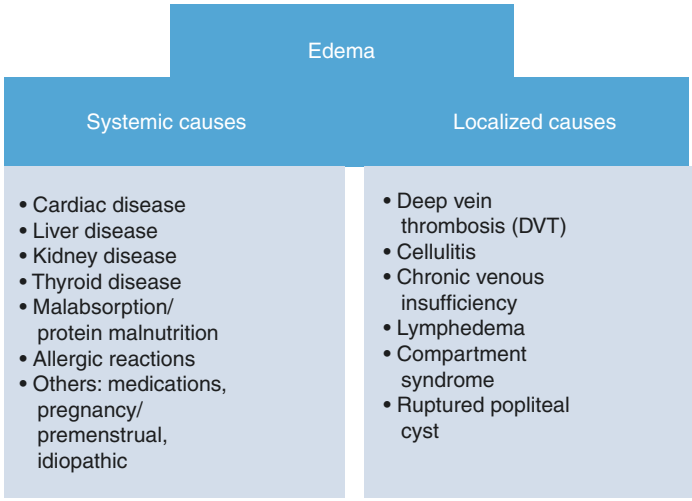

Figure 19.1 Systemic and localized causes of edema

There are two types of lower extremity edema, venous edema and lymphedema. Chronic venous insufficiency is associated with other chronic skin changes such as hyperpigmentation and prominent veins. Some patients with underlying unilateral chronic venous disease might have asymmetric edema. Lymphedema is usually non-pitting, and the skin has a verrucous aspect. Lymphedema can be the result of lymph node dissection. Lastly, obstruction by a tumor or lymphadenopathy can lead to unilateral edema. Also consider in your differential lipedema, a condition in which there is deposition of excess fat in the lower extremities and can be mistaken for edema.

Edema related to systemic conditions is often subacute or chronic and bilateral, affects the lower extremities, and on occasion becomes generalized (Fig. 19.1). Certain clues can orient to the etiology of edema. The presence of jugular venous distention, positive hepatojugular reflux, an S3 gallop, rales, and ascites are features of cardiac disease (e.g., congestive heart failure and pulmonary hypertension). Jaundice, ascites, and asterixis are seen with liver disease, and a frothy urine could be a manifestation of underlying kidney disease. Generalized edema can be seen in a diet deficient in protein or in patients with malabsorption. Thyroid disease can result in generalized myxedema as seen in hypothyroidism or pretibial myxedema as seen in hyperthyroidism. Idiopathic edema is a diagnosis of exclusion and may occur in a cyclical fashion.

Key History and Physical Exam

The history should include details about the onset of edema (acute or chronic), if unilateral or bilateral, if it involves the upper extremities or lower extremities or is generalized, and if it is positional (Fig. 19.2) [4]. Associated symptoms should also be assessed, with emphasis on local skin changes and presence or absence of pain. The clinician should also inquire about the presence of other systemic symptoms such as fever,

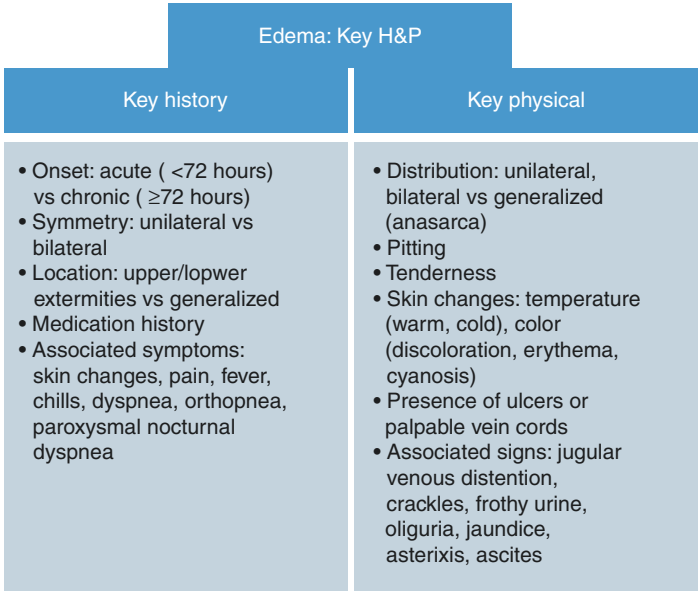

Figure 19.2 Key history and physical in the evaluation of edema

chills, or weight loss as well as those suggestive of hypervolemia. The medication list, including over-the-counter remedies, should be thoroughly reviewed given that commonly used medications can be associated with edema (Table 19.1).

Physical examination should focus on evaluating the distribution and severity of edema (Fig. 19.2) [4]. The physician should evaluate for the presence or absence of pitting by pressing with his or her finger continuously for 5 s. Pitting refers to the movement of fluid in the interstitial space when pressure is applied. The categorization of edema is based on a scale of 1–4+, and it is useful to describe the distribution of the pitting (e.g., pedal or pretibial). Edema can be found in the lower extremities in ambulatory patients and in dependent areas in those who are confined to a bed (e.g., sacrum). Non-pitting edema is suggestive of lymphedema or thyroid disease (pretibial myxedema).The Kaposi-Stemmer sign refers to the inability to form a fold on the skin at the base of the second toe and is suggestive of lymphedema [2, 8].

Table 19.1 Commonly used medications associated with edema [1, 5–7]

Category	Examples
Antihypertensives	Amlodipine, minoxidil
Corticosteroids	Prednisone, fludrocortisone
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen
Antidiabetic drugs	Pioglitazone
Others	Estrogen/progesterone, testosterone

The skin should be thoroughly evaluated describing its color, temperature, and presence of ulcers or palpable vein cords. In patients with deep vein thrombosis, a larger calf circumference is a useful finding. Homan's sign, which consists of calf pain elicited by foot dorsiflexion, is not reliable. The systemic evaluation should include the evaluation for jugular venous distention, hepatojugular reflux, rales on lung examination, sacral edema, and ascites.

Decision-Making/Treatment

Edema is a common manifestation of many disease states. In those patients with findings of acute-onset, painful unilateral edema with risks for hypercoagulability concerning for DVT (Fig. 19.3), a D-dimer and venous ultrasound can be part of the initial evaluation depending on the level of clinical suspicion [9]. In patients presenting with acute bilateral leg edema, the possibility of DVT must still be considered. The presence of bilateral DVT can be associated with malignancy. If the clinical probability of DVT is high, proceed with further testing. Tests evaluating serum creatinine, liver function, and serum albumin level along with urinalysis for proteinuria, presence of white blood cells, red blood cells, and casts are useful initial labs in patients with bilateral or generalized edema (Fig. 19.4). Thyroid-stimulating hormone can also be included if there is suspicion for thyroid disease. Duplex

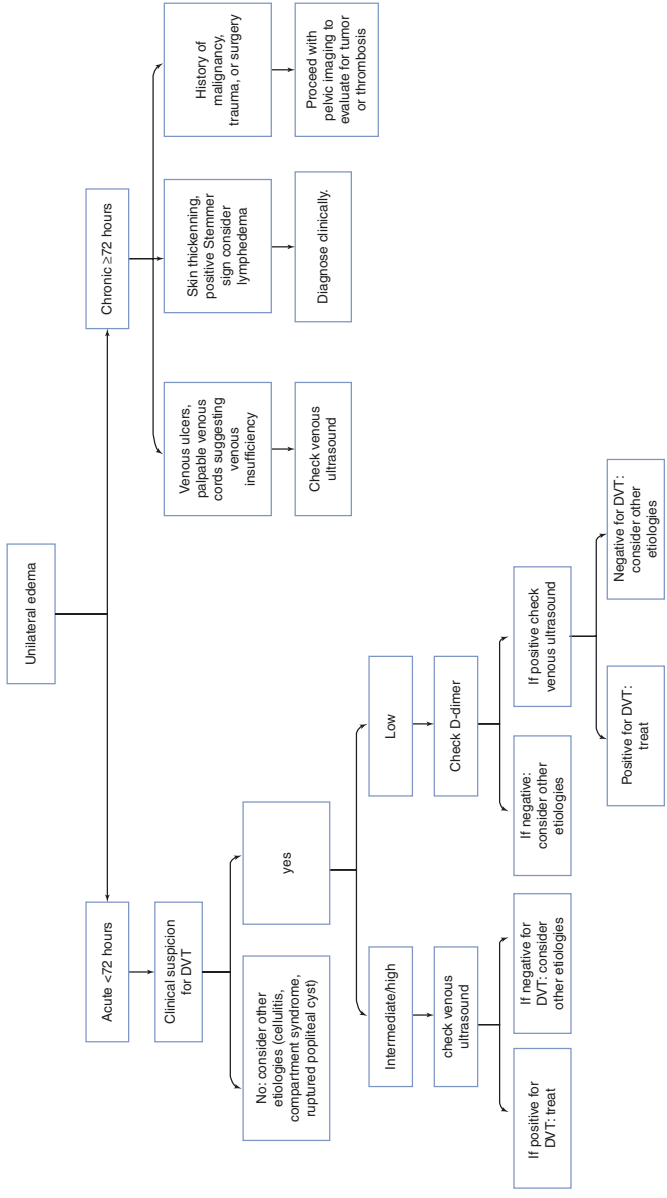

FIGURE 19.3 Clinical approach for the patient presenting with unilateral edema

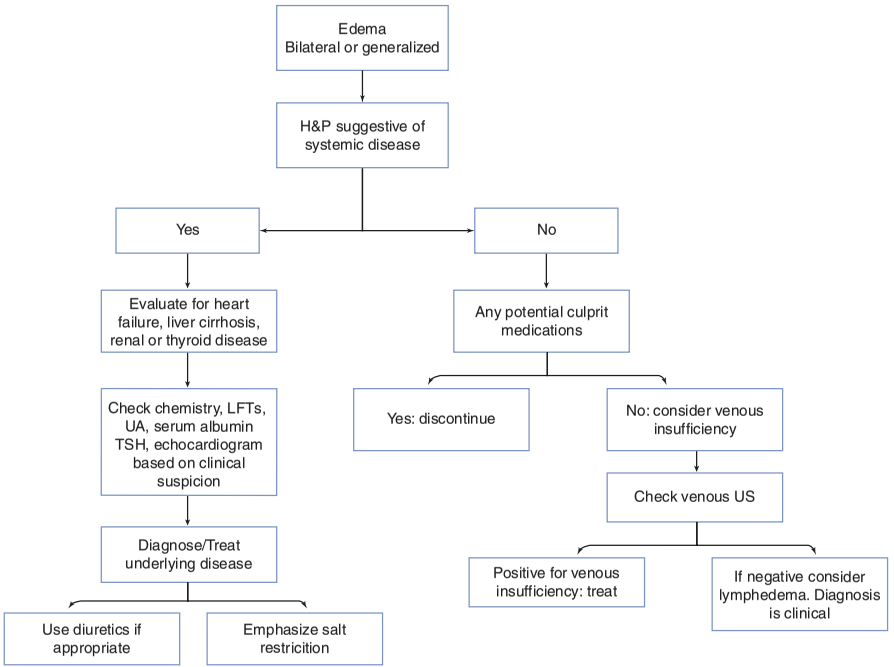

FIGURE 19.4 Clinical approach for the patient presenting with bilateral or generalized edema

ultrasonography can also reveal if there is chronic venous insufficiency and a transthoracic echocardiogram (TTE) could be obtained if history and physical are concerning for heart failure. Ultrasound examination of the inferior vena cava diameter and collapsibility may also provide information about hypervolemia.

By directing therapy at correcting the underlying capillary hemodynamic disturbance, development of edema can be stopped or reversed. Lifestyle and dietary modification in conjunction with pharmacotherapy are useful in the long-term management. For the common systemic causes, treatment of the underlying condition is indicated. For those with chronic venous insufficiency, mechanical therapies such as leg elevation and compression stockings, as well as judicious diuretic therapy, are useful, although caution should be taken in those with peripheral arterial disease. Deep venous thrombosis is treated with anticoagulation therapy and cellulitis with antibiotics. In medication-induced edema, the culprit medication should be discontinued if possible, and in those with heart failure, cirrhosis, and nephrotic syndrome, cautious use of diuretics and salt restriction can be initiated. Caution to avoid volume depletion with diuretics must be exerted. Patients should be monitored for electrolyte disturbances and changes in urea and serum creatinine, watching for signs of volume depletion. For patients with nephrotic syndrome, higher doses of diuretics might be required. For those with diuretic resistance, the use of diuretic combinations could be required.

Clinical Pearls

- A thorough history and physical examination are essential.
- Chronic venous insufficiency and cellulitis have common manifestations: peripheral edema, increase in skin temperature, and erythema. Have in mind that cellulitis is usually a unilateral process.

Don't Miss This!

- Deep vein thrombosis presents with acute limb swelling in a patient with risk factors (e.g., immobilization) but could be bilateral in patients with malignancy.
- Compartment syndrome presents with acute limb swelling, tense skin, and decreased peripheral pulses.
- Heart failure presents with peripheral edema ± pulmonary edema, jugular venous distention, and ascites.
- Recheck medication list and do not forget over-the-counter medications: common things are common!
- Think of central venous stenosis causing upper extremity edema in patients with history of central catheter placement.
- Facial edema and dilated neck veins are findings of superior vena cava syndrome.

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Part V
Dermatologic

Chapter 20
Rash

Alexander Howell and Karthik Krishnamurthy

Introduction

Rashes are common problems encountered in all facets of healthcare that often represent a diagnostic conundrum, even at times to the most experienced dermatologist. Many conditions produce rashes that appear very similar clinically, and the differences distinguishing them are often subtle, or only apparent on histopathology. It is important that the correct differential diagnosis be made initially. Many conditions can be exacerbated by incorrect treatments or delay of therapeutic intervention, leading to significant morbidity in some cases and, rarely, mortality. When approaching rashes, it is helpful to generate a good differential diagnosis by categorizing the rash based on its reaction pattern. Presented here is an algorithmic approach to rashes that begins with five previously described reaction patterns: papulosquamous, eczematous, vascular, dermal, and vesiculobullous [1]. Each reaction pattern is then subcategorized based on nuances in the appearance, texture, and symptoms of various skin conditions.

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Decision-Making/Differential Diagnosis

The initial step in approaching a rash is to create a detailed description of the rash. A good description includes primary morphology, secondary change, color, shape, configuration, and distribution (see H and P).

Next, categorize the reaction pattern based on your description:

- *Papulosquamous rashes* are red scaly rashes.
- *Eczematous rashes* are red and itchy and can have scale, crust, and lichenification (accentuation and thickening of skin markings).
- *Dermal rashes* are rashes with no surface (or epidermal) change.
- *Vascular rashes* are red and may be blanching or non-blanching.
- *Vesiculobullous rashes* are rashes with blisters of varying sizes.

In general, consider common conditions first while at the same time ruling out life-threatening conditions promptly (i.e., severe drug reactions such as Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], drug reaction with eosinophilia and systemic symptoms, urticaria with angio-edema, staphylococcal scalded skin syndrome [SSSS], toxic shock syndrome [TSS] , erythroderma, meningococcemia, rocky mountain spotted fever [RMSF], bacterial endocarditis, necrotizing fasciitis, etc.) [2, 3].

Papulosquamous

Generally speaking, this reaction pattern includes rashes with red, scaly papules and plaques.

Psoriasiform

Psoriasis. Well-demarcated, red plaques with thick overlying scale. Common locations include extensor surfaces (knees, elbows), scalp, palms, and soles. Nail findings can aid in the diagnosis and include pitting, oil spots, and onycholysis (Fig. 20.1).

Seborrheic dermatitis. Erythema with overlying greasy scale in a "seborrheic distribution" (oil- and hair-bearing areas). Associated with HIV, Parkinson's disease, and other neurologic conditions [4].

Pityriasis rubra pilaris. Reddish-orange scaly plaques, keratotic follicular papules, or palmoplantar keratoderma. Distinct areas of uninvolved skin referred to as "islands of sparing" are characteristic.

Tinea corporis. Annular or ring-shaped red, scaly plaques. Raised border has more scale than the clearer center of the lesion [4].

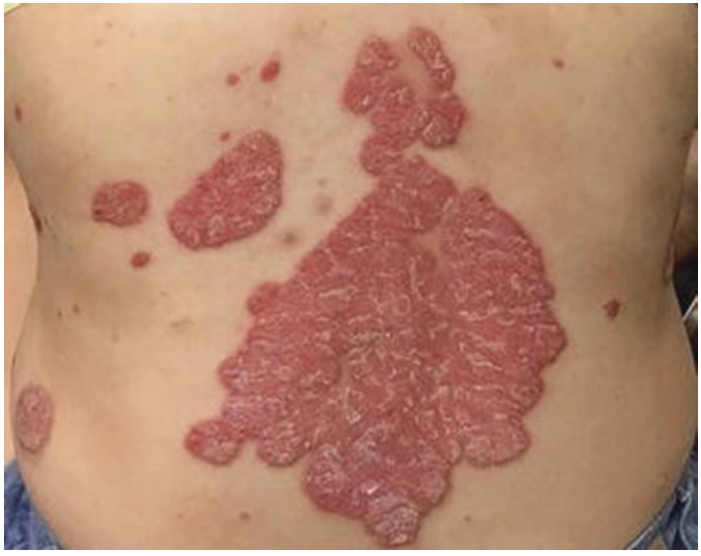

FIGURE 20.1 Plaque psoriasis. Thick, red plaques with sharply demarcated borders and overlying silvery scale

Pityriasiform

Pityriasis rosea. Oval-shaped pink to red scaly thin plaques in "Christmas tree" distribution along the body folds. Often a herald patch appears a few days before the other smaller lesions. Located mostly on the trunk, it can involve extremities. This can occur on the face in African Americans.

Secondary syphilis. Small red to brown scaly papules with involvement of the palms and soles.

Tinea versicolor. Tan to red or hypopigmented thin plaques with fine scale. These are typically located on the upper chest, upper back, and neck.

Lichenoid

Lichen planus (*LP*) five Ps. Purple, polygonal, planar, and pruritic plaques. "Wickham striae" may be present. Lower extremities are a common location, but some people have mucosal and penile lesions. Drug-induced LP is associated with NSAIDs, diuretics, ACE inhibitors, and beta-blockers [4] (Fig. 20.2).

Erythroderma

Erythroderma is generalized erythema and scaling that affects >90% of the body surface area. The underlying causes include preexisting dermatoses (atopic dermatitis, psoriasis, seborrheic dermatitis), cutaneous T-cell lymphoma, or drug reactions [4] (Fig. 20.3).

Eczematous

1. *Acute eczema*. Weeping, vesicular erythematous papules and plaques that are very itchy. Geometric or linear configuration indicates an "outside job" and is a clue to diagnosis [1]. Includes acute allergic/irritant contact dermatitis and dyshidrotic eczema.

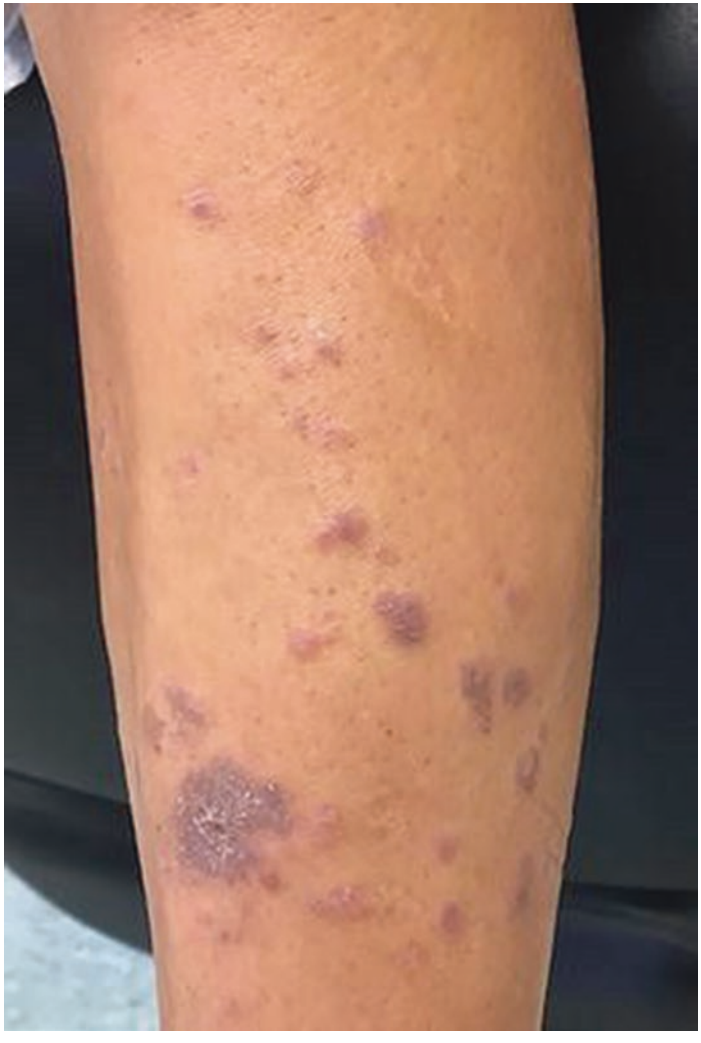

FIGURE 20.2 Lichen planus. Purple, polygonal, planar plaques on the anterior lower extremity

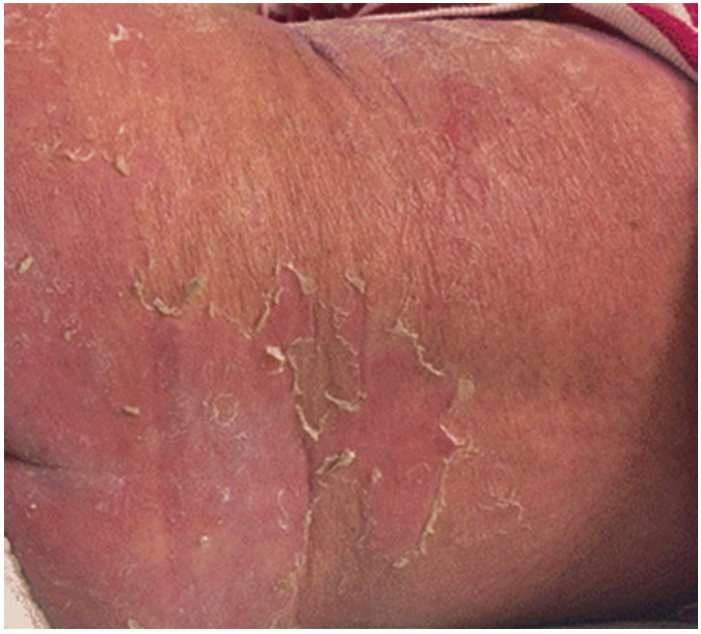

FIGURE 20.3 Erythroderma. Generalized erythema and exfoliative scaling in a patient with underlying psoriasis

2. *Subacute eczema*. Eczematous lesions that progress, forming scaly crust.
3. *Chronic eczema*. Characterized by lichenification, hyperpigmentation, and thicker scaly plaques.

Atopic dermatitis. Common in children, but can also be seen in adults. Located in flexural areas. It is associated with asthma, allergies, and an "itch-scratch" cycle. A diagnostic clue is that the middle part of the back (where the patient cannot reach to scratch) will be spared (Fig. 20.4).

Stasis dermatitis. Typically seen on the lower extremities in elderly individuals. Underlying venous insufficiency, varicose veins, and edema are present. Hyperpigmentation occurs from hemosiderin deposition. Itching and overlying scale occurs.

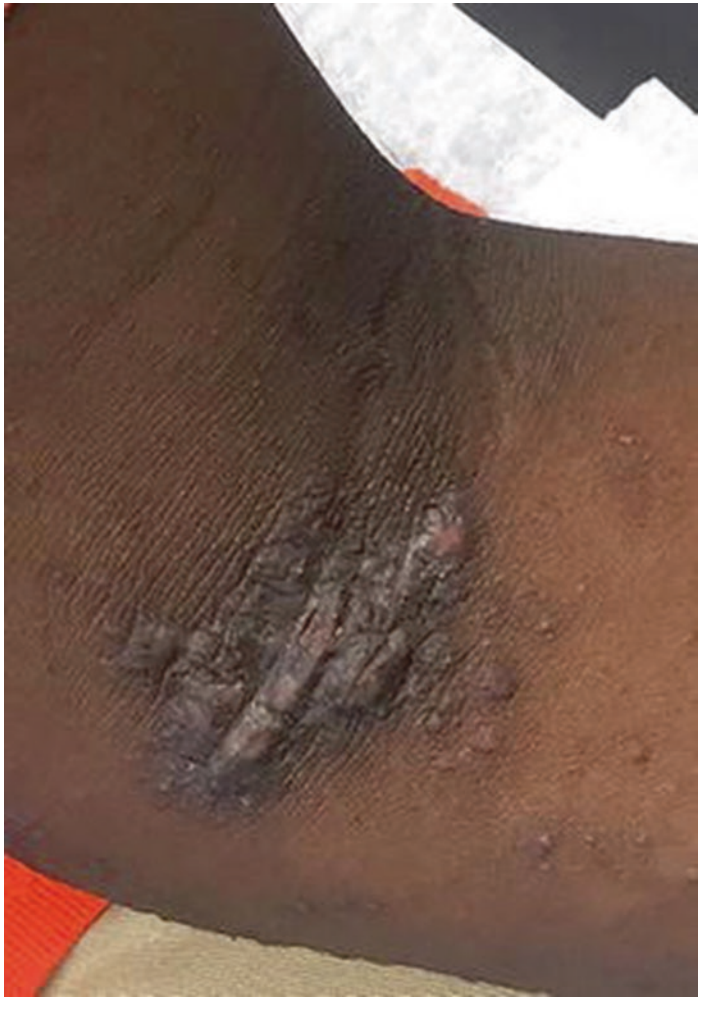

FIGURE 20.4 Chronic eczema. Lichenification and hyperpigmented papulonodules in the antecubital fossa of a child with atopic dermatitis

Dermal

1. *Subcutaneous.*

   (a) *Panniculitis.* Erythematous deep nodules:
   - *Septal*: superficial thrombophlebitis, erythema nodosum, or cutaneous polyarteritis nodosa.
   - *Lobular*: erythema induratum, Crohn's disease, calciphylaxis, lupus panniculitis, or pancreatic panniculitis (Fig. 20.5).

   (b) *Cellulitis.* Erythema, edema, warmth and pain with/without fever, and lymphadenopathy.

   (c) *Necrotizing fasciitis.* Erythema, edema, warmth and pain out of proportion to skin findings initially. Rapid progression to a gray-blue color in ill-defined patches with "woody" induration. Hemorrhagic bullae may develop. Treatment is emergent extensive surgical debridement. Termed *fournier gangrene* if perineum and genetalia are involved.

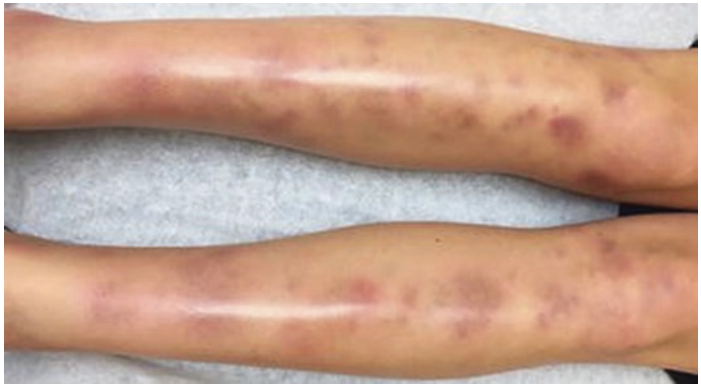

FIGURE 20.5 Erythema nodosum. Tender, erythematous nodules over the shins in a young female taking oral contraceptive pills

2. Inflammatory
   (a) *Lupus erythematosus.* Malar erythema (spares nasolabial fold) with confluent erythema and edema or maculopapular lesions in sun-exposed areas. Oral ulcers may be present.
   (b) *Granuloma annulare.* Groups of 1–2-mm papules in an annular arrangement often found on distal extremities, hands, feet, fingers, and extensor aspects of the arms and legs.
   (c) *Sarcoidosis.* Purple-red or brown indurated circular plaques. Erythema nodosum may be present.
3. Infectious
   (a) *Erysipelas.* Well-demarcated fiery-red indurated, tense, often shiny, plaque that is most often on the lower extremities or face. Abrupt demarcation from healthy skin is a classic clinical sign.
   (b) *Deep fungal infections.* Often rapidly spreading patch, plaque, nodule, or abscess often with necrotic center, ulcers, or sinuses. Causes include histoplasmosis, blastomycoses, coccidioidomycoses, and cryptococcus.
   (c) *Atypical mycobacterium, sporotrichosis, and cat-scratch disease.* Linear subcutaneous nodules with unilateral lymphadenitis.
4. Proliferative

   This category includes various benign and malignant dermal neoplasms or proliferations. The list of dermal proliferations is long and includes various cysts, adnexal tumors (eccrine gland, apocrine gland, hair tumors), tumors derived from collagen/elastin, muscle cells, nerve cells, blood vessels, and melanocytic lesions. Finally, what is referred to as the "purple plum" differential is considered, which includes amelanotic melanomas, cutaneous metastases, sarcomas, vascular tumors (Kaposi sarcoma and angiosarcoma), lymphomas, and leukemia cutis.

5. Depositional

   A group of unrelated disorders characterized by deposition of substances within the dermis. This is broken down into the type of substance deposited: lipid (xanthomas), mucin (myxedema, granuloma annulare, necrobiosis lipoidica diabeticorum), amyloid (primary, secondary, macular, or nodular), calcium (calciphylaxis, dystrophic, metabolic), or urate (gout).

Vascular

Vascular rashes are red in color and are distinguished first by whether or not they are blanching due to vasodilation. Purpuric rashes are non-blanching due to red blood cell extravasation. Palpable purpura indicates vasculitis.

1. *Urticaria*. Classic hive or wheal appearance: edematous, blanching erythematous plaques due to a type I hypersensitivity.
2. *Toxic erythema*. Diffuse and confluent blanching erythematous macules and papules. *These can be deadly*. Etiologies include viral exanthems, drug eruptions, and the following:
   (a) *Scarlet fever.* Features multiple 1–2-mm punctate papules with sandpapery feel. Treat with penicillin or erythromycin.
   (b) *SSSS.* Diffuse yellow-red tender erythema that progresses to large, flaccid bullae with desquamation. Treat with penicillins, cephalexin, cefazolin, or TMP-SMX.
   (c) *TSS.* Fever >102 °F, rash, late desquamation, strawberry tongue, pharyngeal redness, and conjunctivitis. Treat with clindamycin, vancomycin, or nafcillin.
   (d) *Kawasaki disease.* Polymorphous rash, strawberry tongue, conjunctivitis, redness and scaling of palms and soles, and cervical adenopathy. Treat with aspirin and IVIG [5].

(e) *Stevens-Johnson syndrome/toxic epidermal necrolysis* (*SJS/TEN*). Diffuse erythema, bullae that become necrotic followed by diffuse desquamation of the skin. Commonly implicated drugs include NSAIDs, penicillins, sulfa drugs, anticonvulsants, barbiturates, and allopurinol.

3. *Erythema multiforme*. Targetoid red papules with dusky center that can be bullous. Involves palms and soles, unlike many other rashes.
4. *Vasculitis*. Palpable purpura. Can be vesicular or bullous [6] (Fig. 20.6).

   (a) *Hypersensitivity*. Symmetric. Infection (HCV, group A *Streptococcus* [GAS], autoimmune disease, drug, malignancy, and Henoch-Schonlein purpura.
   (b) *Septic*: Asymmetric, often involving acral surfaces. Meningococcemia, pseudomonas, gonococcemia, and GAS.

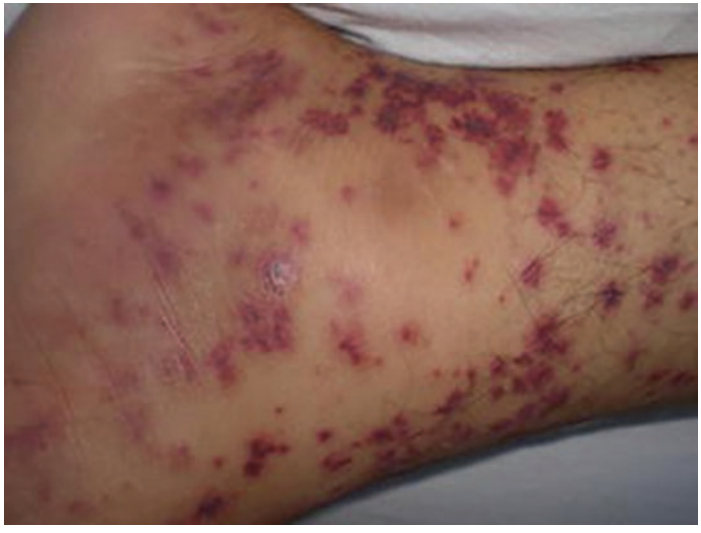

FIGURE 20.6 Palpable purpura on the lower extremity indicating leukocytoclastic vasculitis

5. *Vasculopathy*. Ranges from petechiae to purpura with ulceration and atrophy. Etiologies include idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hypercoagulable states, renal failure, hereditary platelet disorders, scurvy, DIC, and lymphoproliferative states (Waldenstrom macroglobulinemia, leukemias, myeloma) [6].
6. *Annular erythema*. *Erythema chronicum migrans* (*ECM*). Associated with Lyme disease. An erythematous ring around a central punctate erythematous papule (indicates tick site) spreading outwardly with annular appearance.

Vesiculobullous

Blistering rashes with either intraepidermal or subepidermal bullae and a background of inflammatory or noninflammatory skin. Various conditions already mentioned can also blister, including meningococcemia, contact dermatitis, vasculitis, erythema multiforme, and SJS/TEN [7].

Infectious

Herpes simplex virus. Grouped vesicles on an erythematous base. Vesicles crust over as they heal.

Herpes zoster. Grouped painful/burning herpetic vesicles on an erythematous base in a dermatomal distribution. Pain often precedes rash (Fig. 20.7).

Coxsackie. Vesicles on the tongue or buccal mucosa, hands, and feet, including the palms and soles. Uncommonly, the buttocks and genitalia are involved. Vesicles are tender and may ulcerate, but are usually not pruritic.

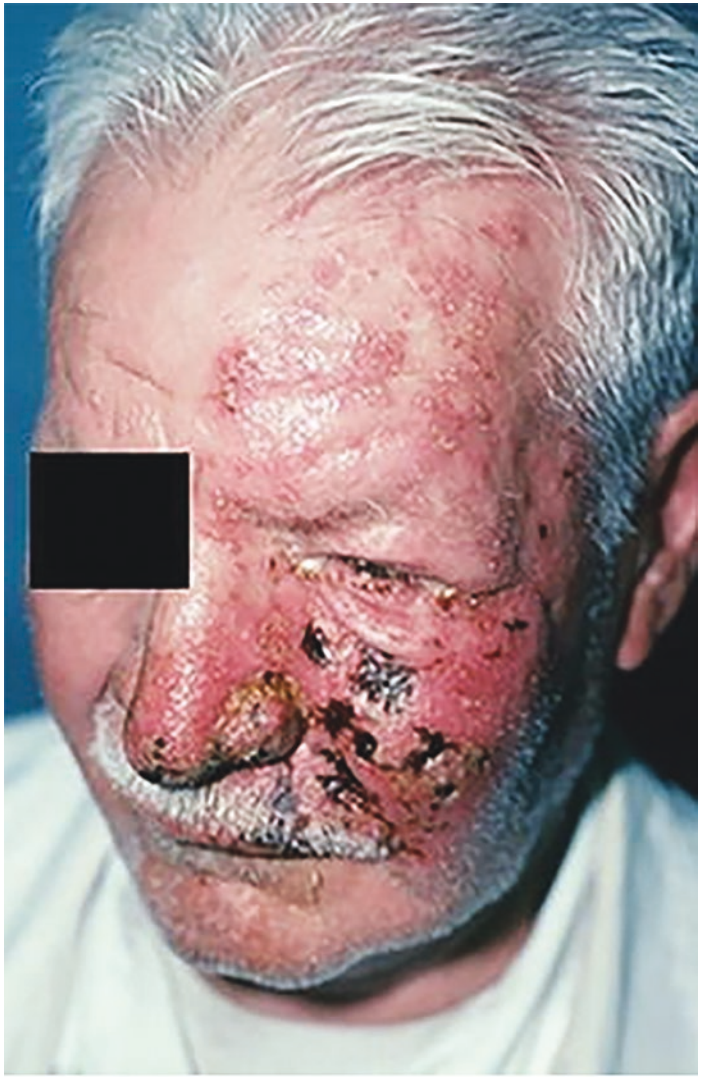

FIGURE 20.7 Herpes zoster. Vesicles and crusting involving the trigeminal nerve (V1 and V2) distribution

Autoimmune, Intraepidermal

Pemphigus vulgaris (*PV*). Flaccid blisters with crust and erosions present. Oral involvement is common. Positive Nikolsky sign.

Autoimmune, Subepidermal

Bullous pemphigoid. Common condition seen in the elderly. Tense bullae that do not rupture easily. Common locations include trunk and flexural areas (Fig. 20.8).

Noninflammatory

Porphyria cutanea tarda. Acral blisters that worsen with sun exposure, alcohol use, and estrogen [8].

Miliaria crystallina. Numerous small superficial vesicles in intertriginous areas or head/neck in infants caused by obstruction of the sweat glands. Can also be seen in febrile adults.

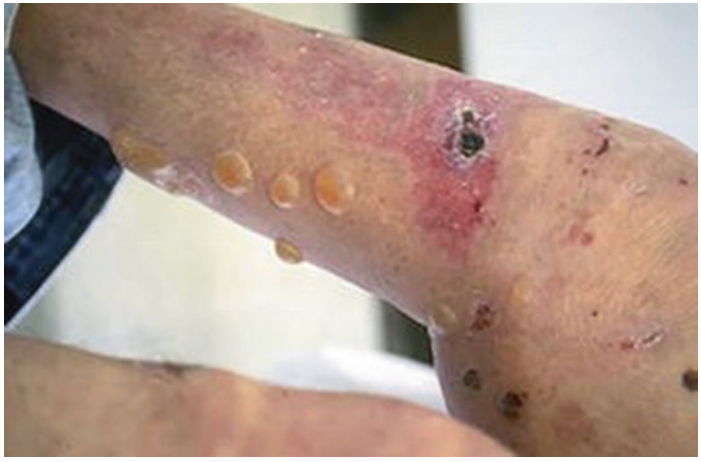

FIGURE 20.8 Bullous pemphigoid. Tense bullae on the lower extremities. (Previously published in Buka B, Uliasz A, Krishnamurthy K. Buka's Emergencies in Dermatology. New York: Springer; 2013)

History and Physical Examination

History

- Duration and history of rash: acute vs. chronic, symptoms (itchy, painful, progression of lesion color/texture and distribution, drainage, fever), aggravating and alleviating factors, previous treatments attempted including topical and over-the-counter formulations.
- Description: location of rash, color, texture.
- Medical history: recent changes in health problems, recent illnesses or hospitalizations, new medications.
- Social history: recent travel, contact with plants or bodies of water, sick contacts, pets, arthropod bites, occupation (chemical exposures), sexual history.
- Environmental changes: new products including but not limited to perfumes, cosmetics, soaps, shampoos, detergents, hair dye, nail polish, clothing components (nickel in buttons, leather shoes, etc.)

Physical Examination

- Vital signs: presence of fever, signs of hemodynamic instability.
- Gross inspection [4, 9]:
  - *Primary morphology* represents the native initial appearance of the rash and the morphologic terms are described as follows:

    Macule: nonpalpable (flat) lesion less than 1 cm.
    Patch: nonpalpable (flat) lesion greater than 1 cm.
    Papule: palpable (commonly elevated, rarely depressed) lesion less than 1 cm.
    Plaque: palpable (commonly elevated, rarely depressed) lesion greater than 1 cm.
    Nodule: palpable (elevated) lesion often greater than 1 cm involving the dermis and subcutaneous tissues.
    Wheal: transient elevation of the skin due to dermal edema.
    Vesicle: fluid-filled lesion less than 1 cm.
    Bulla: fluid-filled lesion greater than 1 cm.

Pustule: lesion filled with purulent fluid from onset.
Furuncle: abscess involving a single follicular unit.
Carbuncle: abscess involving multiple follicular units.

- *Secondary change* represents the effects of exogenous forces or temporal change to the primary lesion and they are described as follows:
  Excoriation: exogenous injury to the epidermis (common following scratching).
  Scale: accumulation of the stratum corneum (hyperkeratosis).
  Crust: dried serum, blood, or purulence overlying the lesion.
  Erosion: partial loss of the epidermis.
  Ulceration: loss of the full epidermis and occasionally the dermis or subcutis.
  Fissure: linear cleft in the skin.
  Lichenification: accentuation of the skin lines as a result of epidermal thickening (often due to chronic rubbing or scratching).
- *Color*: erythematous, hyperpigmented/hypopigmented, flesh-colored, red-brown, violaceous, purpuric, dusky (dark purple/gray that suggests necrosis).
- *Shape:* annular (circular with central clearing), nummular (circular with central involvement), ovoid, linear, serpiginous, targetoid, polycyclic (coalescing annular), arcuate (incomplete annular), polymorphous (many shapes).
- *Distribution*: generalized, central, peripheral, palms/soles ("acral"), flexural vs. extensor surfaces, unilateral vs. symmetric, photo-distributed (sun-exposed skin) vs. photoprotected skin (buttocks, hips, etc.), intertriginous, mucosal involvement.
- *Configuration*: linear/geometric (suggests outside influence), dermatomal, grouped/coalescing.
- *Texture*: soft, firm, fleshy, indurated, fluctuant.
- *Patterns*: follicular, morbilliform ("measles-like" aka maculopapular), reticular ("net-like"), monomorphic, guttate (drop-like).

- Diagnostic procedures:
  - Potassium hydroxide (KOH) prep: identifies dermatophyte infection.
    Positive test: presence of hyphae (long, slender, refractile filaments that cross multiple cell walls). Tinea versicolor is diagnosed by presence of "spaghetti and meatballs" appearance, which represents hyphae and spores [3].
  - Mineral oil prep: identifies scabies or Demodex mites.
    Positive test: observe mite, eggs, or feces (scybala) for scabies. Observe mite for Demodex. Mineral oil used.
  - Wood's lamp (365 nm) [4]:
    Findings in different skin conditions:
    - Vitiligo: milky white appearance.
    - Tinea versicolor: yellow or orange glow.
    - Tinea capitis: *Microsporum* species fluoresce blue-green, *Trichophyton schoenleinii* fluoresces dull blue.
    - Erythrasma: coral-pink color due to *Corynebacterium.*
    - *Pseudomonas*: fluoresces green.
    - Porphyria: red-pink fluorescence of skin.
  - Nikolsky sign: positive if lateral pressure causes shearing of the epidermis from the dermis. This indicates an intraepidermal process.
  - Asboe-Hansen sign: positive if gentle pressure on the blister causes lateral expansion of the blister. This also indicates an intraepidermal process.
  - Diascopy: pressing on a lesion with a glass slide to see whether or not redness blanches out. Purpura is non-blanching often indicating vasculitis.
  - Skin biopsy: rashes not responding to conventional treatment require a biopsy. For autoimmune conditions, two punch biopsy samples should be taken, one for H&E and one for direct immunofluorescence (DIF). The DIF specimen should be obtained from uninvolved perilesional skin for suspected immunobullous processes.
- Treatment: Please see diagnostic and treatment (Figs. 20.9, 20.10, 20.11, 20.12, 20.13, and 20.14).

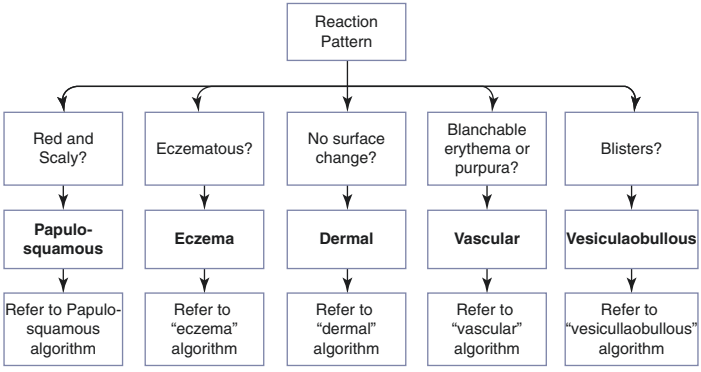

FIGURE 20.9 Approach to rashes based on clinical reaction patterns

Clinical Pearls

- A broad differential diagnosis based on a rash's reaction pattern is helpful in diagnosing the rash.
- Consider common rashes first and rule out life-threatening rashes quickly.
- Perform a KOH on most scaly rashes.
- Erosion and/or ulceration can represent an initial vesiculobullous eruption.
- Punch biopsies (3–5 mm) should be used for nonresponding or undiagnosed rashes, and a DIF should be performed for vesiculobullous eruptions.DisclaimerThis research was supported (in whole or part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this presentation represent those of the author and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

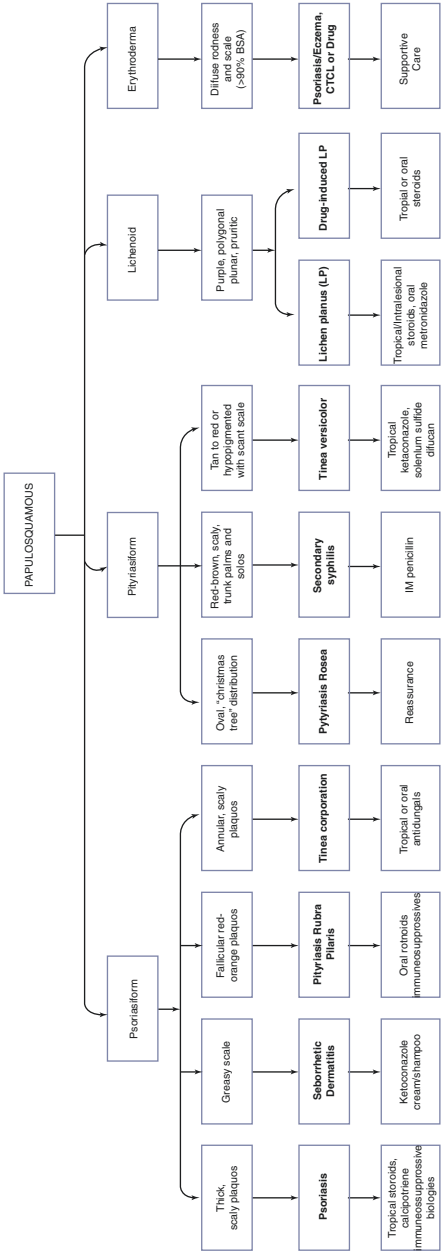

FIGURE 20.10 Algorithm for rashes with papulosquamous reaction patterns

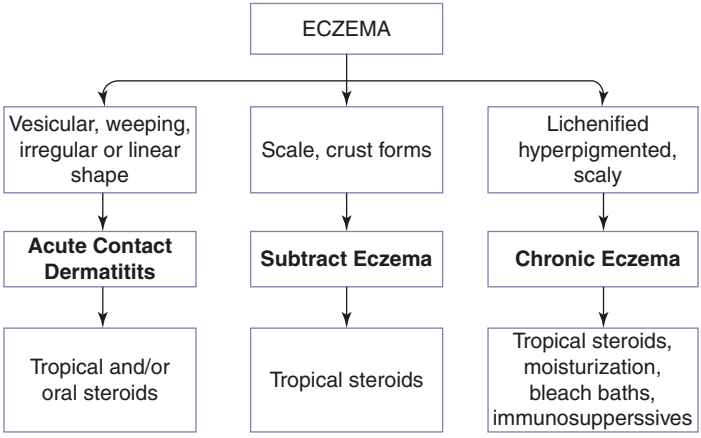

FIGURE 20.11 Algorithm for rashes with eczematous reaction patterns

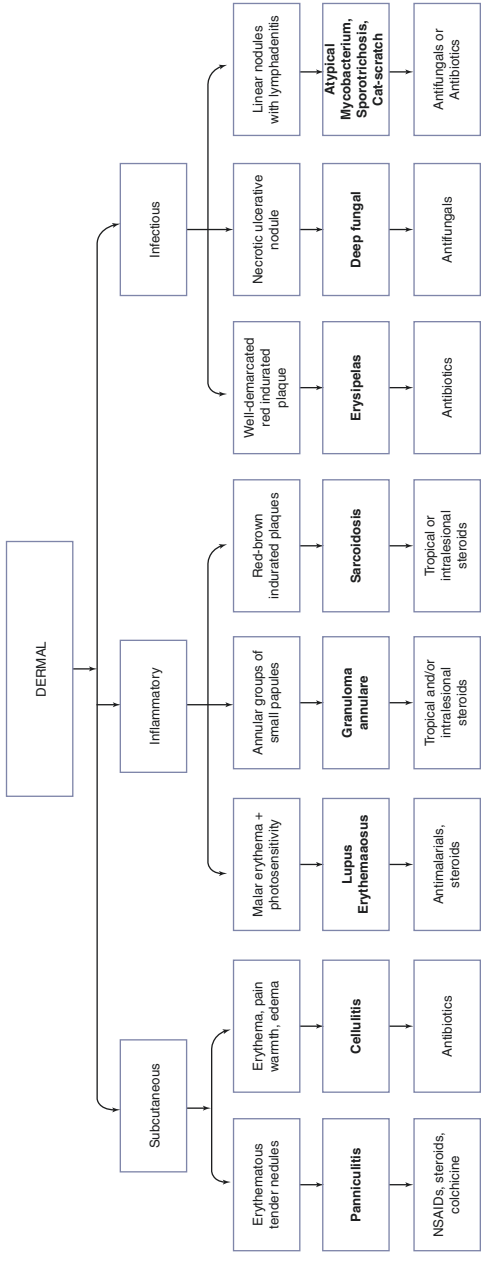

FIGURE 20.12 Algorithm for rashes with dermal reaction patterns

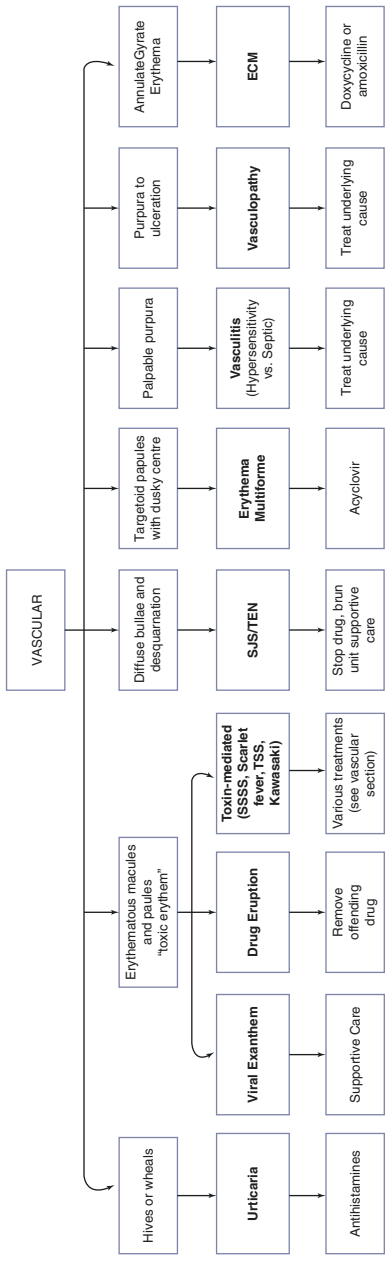

FIGURE 20.13 Algorithm for rashes with vascular reaction patterns

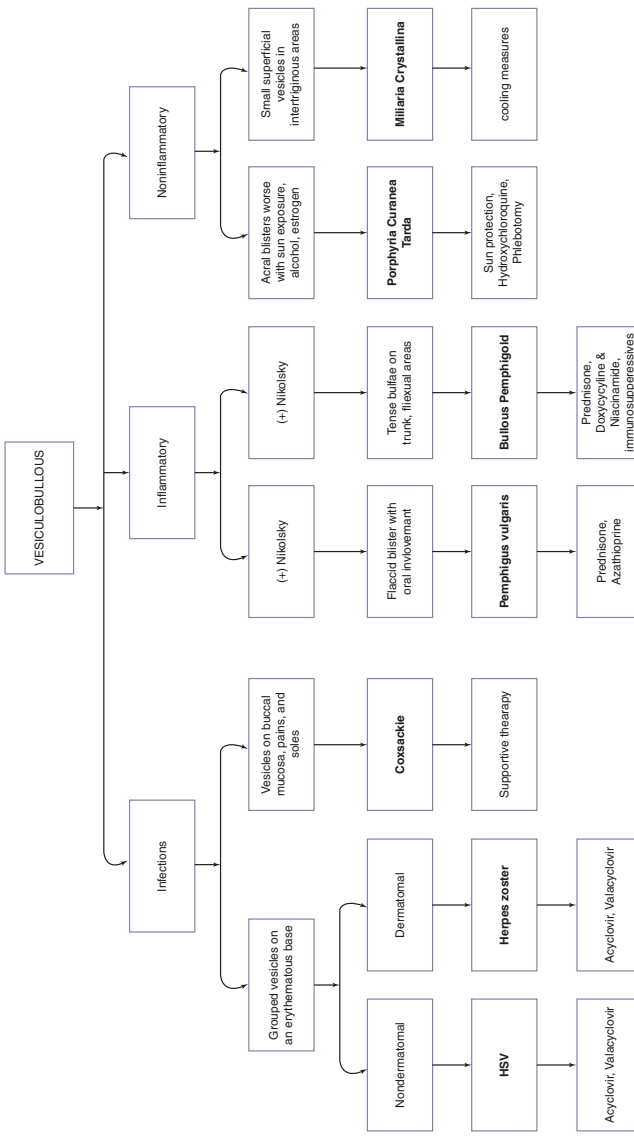

FIGURE 20.14 Algorithm for rashes with vesiculobullous reaction patterns

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Chapter 21
Alopecia

Clara Barranco and Karthik Krishnamurthy

Introduction

Alopecia (or hair loss) includes a group of disorders in which there is an absence of hair where it is usually present. More than 35 million men and 21 million women in the USA experience hair loss. The incidence is highest in Caucasians, followed by Asians, African Americans, and Native Americans. Though a common problem, hair loss can cause a considerable amount of emotional and social stress to patients. Moreover, it presents a challenge for practitioners, as there are multiple etiologies with similar clinical presentations.

Understanding the normal hair cycle is key in assessing alopecias. There are three main phases of the hair follicle

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cycle: anagen (active growth), catagen (regression), and telogen (rest). Approximately 85–90% of hair follicles are in the anagen phase, while 10–15% are in the telogen phase, and less than 1% in the catagen phase. There are approximately 100,000 hair follicles on the scalp, and, on average, 50–100 hairs are normally lost every day [1]. Hair loss becomes a clinical problem when there are localized patches of hair loss or when the number of hairs lost daily exceeds the normal amount. Progressive thinning and excessive shedding of the scalp hair are the two most common hair complaints reported [2].

The alopecias are divided into two main categories: scarring (or cicatricial) and non-scarring (or non-cicatricial) alopecias (Fig. 21.1). When assessing a patient with alopecia, it is important to consider the chief complaint as stated by the patient, the chronicity, the age at onset, whether there is a pattern to the areas of hair loss, and if there have been any major stressors, physical or emotional, in the patient's life. Androgenetic alopecia, also referred to as female or male pattern hair loss, is the most common type of hair loss due to hormonal effects at the level of the follicle and is what most patients refer to as "balding." Generalized thinning is most commonly seen in alopecia areata, in which the etiology is autoimmune, or telogen effluvium, in which some physiologic stressor initiates abnormal shedding [2]. Other causes of hair loss include autoimmune conditions, underlying systemic problems like thyroid disease and iron deficiency, infections of the scalp, inflammatory processes, and habitual practices. Regardless of the underlying cause, both physical and psychological stress can exacerbate any form of hair loss.

Alopecia is characterized into scarring and non-scarring categories. Scarring can be divided based on the predominant cell type: lymphocytic, neutrophilic, and mixed. This category includes discoid lupus, central centrifugal cicatricial alopecia, dissecting cellulitis of the scalp, and acne keloidalis. Non-scarring alopecia can be divided based on its distribution. Focally distributed alopecias include alopecia areata, traction alopecia, and trichotillomania. Diffuse distribution includes

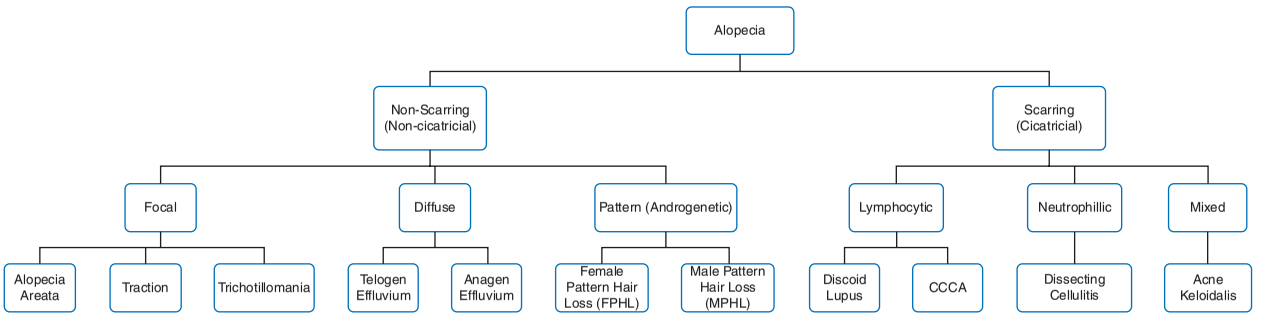

FIGURE 21.1 Hair loss algorithm

telogen effluvium and anagen effluvium. Patterned alopecia, also known as androgenetic, includes female pattern hair loss and male pattern hair loss.

Decision-Making/Differential Diagnosis

The first step to assessing hair loss is to determine whether a scarring or non-scarring process is occurring. Generally speaking, scarring alopecia includes forms of alopecia where the hair follicles are permanently lost. Some alopecias, including alopecia areata, androgenetic alopecia, and traction alopecia, may demonstrate a non-scarring process early in the disease course and permanent hair loss in later stages.

Non-scarring Alopecias

Androgenetic Alopecia

(Synonyms: Male Pattern and Female Pattern Hair Loss [MPHL and FPHL], Common Balding, Hereditary Balding or Thinning)

Androgenetic alopecia represents the most common subtype of the non-scarring alopecias and in fact is the most common cause of hair loss overall. It is due to a genetically determined sensitivity to androgens of the scalp hair follicles [1]. It can begin any time after puberty, when androgens begin to be synthesized [3, 4].

Features:

- Gradual thinning without noticeable shedding.
- Strong genetic disposition, with a high concordance among monozygotic twins.
- Male pattern hair loss: symmetric and progressive, typically affecting the frontoparietal area with frontal recession as well as vertex thinning (Fig. 21.2).

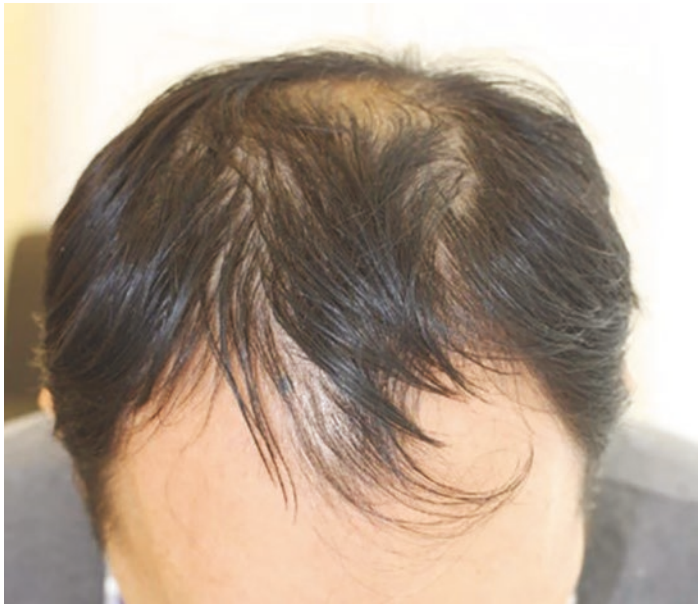

FIGURE 21.2 Classic pattern of androgenetic alopecia in a male involving the bitemporal and crown of the scalp [5]

- Female pattern hair loss: diffuse central thinning of the crown with preservation of the frontal hairline. A "Christmas tree" pattern results with widening of the central part width (Fig. 21.3).
- Treatment options include antiandrogenic medications (Table 21.1).

Focal Hair Loss

Alopecia Areata. This is usually a hair-specific autoimmune phenomenon in which T-cells interact with follicular antigens. It is characterized by abrupt onset usually before the second decade [2]. Alopecia areata can be associated with other

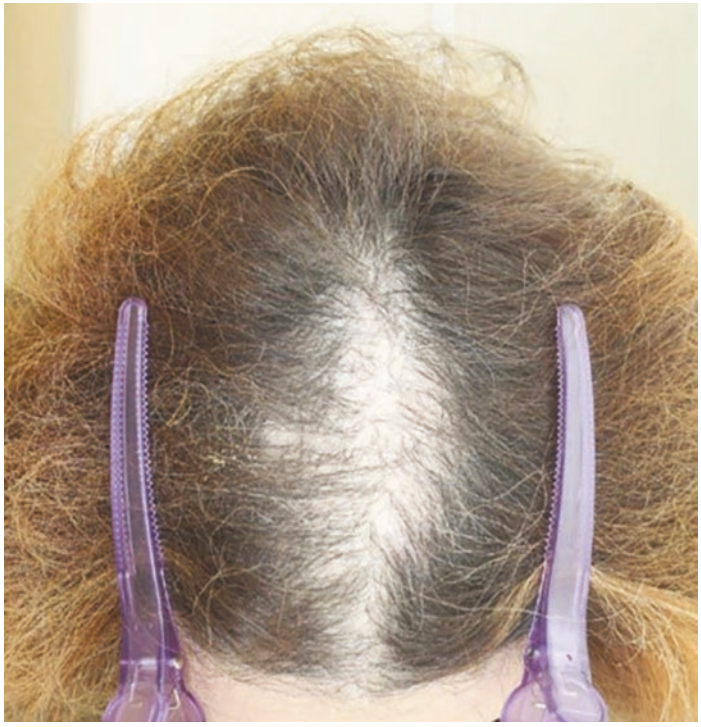

Figure 21.3 Classic "Christmas tree" pattern seen in androgenetic alopecia in a female [5]

Table 21.1 Non-scarring alopecia treatment

Androgenetic alopecia	• Minoxidil 5% topical solution (1 mL BID) • Finasteride 1 mg/day × at least 3 months (with oral contraceptives) • Spironolactone 100–200 mg/day • Surgical hair transplant

Table 21.1 (continued)

Alopecia areata	• Intralesional steroid 2.5–5 mg/mL (0.5–1-cm intervals) • Topical clobetasol propionate 0.05% ointment, desoximetasone 0.25% cream, or betamethasone valerate foam BID • Diphencyprone (DCP) and squaric acid dibutyl ester (SADBE): 0.001% for 2 weeks and gradually increase weekly over time (0.01%, 0.1%, 0.2%, 0.5%, 1%, and 2%) • Topical minoxidil • Topical anthralin • Systemic corticosteroids (for totalis or universalis): 40 mg triamcinolone IM monthly or daily oral prednisone tapered over 6–8 weeks
Trichotillomania	• Behavioral modification therapy, hypnosis, insight-oriented therapy • Clomipramine 25 mg daily, gradually increase to 100 mg/day (divided with meals) over 2 weeks
Telogen effluvium	• Treat underlying thyroid or iron deficiency • Reassurance
Scarring alopecia treatment	
Discoid lupus Erythematosus	• Oral hydroxychloroquine. • Topical, oral, or intralesional corticosteroids.
Central centrifugal Cicatricial alopecia	• Combination of doxycycline or minocycline + topical clobetasol or fluocinonide.
Dissecting cellulitis	• Oral isotretinoin (0.5–1.5 mg/kg daily until 4 months after achieving a clinical remission).
Acne keloidalis	• Doxycycline + potent topical corticosteroids.

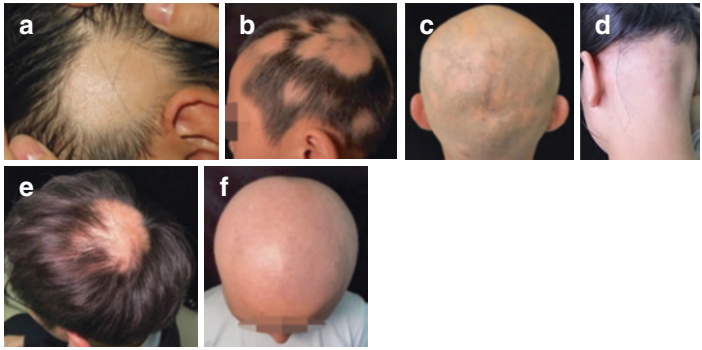

FIGURE 21.4 Clinical variants of alopecia areata (AA). (**a**) Classic round patch of hair loss seen in alopecia areata. (**b**) Multiple round patches of hair loss. (**c**) Reticulate pattern of AA. (**d**) Ophiasis pattern: band-like loss of hair across the temporal and occipital scalp. (**e**) Sisaipho pattern. (**f**) Alopecia universalis [7]

autoimmune diseases, including Hashimoto's thyroiditis, vitiligo, inflammatory bowel disease, and type I diabetes [6] (Fig. 21.4).

Features:

- Typically presents as discrete bare patches of hair loss, in a patchy or multifocal distribution.
- Other presentations include:
- Alopecia totalis: loss of all scalp hair.
- Alopecia universalis: loss of all scalp and body hair.
- Ophiasis pattern: band-like pattern of hair loss that occurs along the periphery of the temporal and occipital scalp.
- Alopecia involving the beard area.
- Multiple treatment options are available, including but not limited to corticosteroids, topical immunotherapy (SADBE, Table 21.1), excimer laser therapy.

*Traction Alopecia***.** Occurs due to physical stress on the hair follicle secondary to tight hairstyles, including ponytails, braids, and hair weaves:

- Hair thinning mainly noted along the marginal hairline—frontally, temporally, and occipitally [2]
- Mostly affects African Americans.

Trichotillomania. Can have various presentations, but there will be rough, irregular patches of hair loss with broken or twisted hairs on closer examination. It is a result of intentional pulling of hair from the scalp [1]:

- Onset in childhood and more commonly seen in females (4:1 ratio) [8].
- Grouped with DSM IV OCD disorders.
- Patients may pull hairs out from other hair-bearing areas such as the eyebrows, eyelashes, face, extremities, and pubic area.
- Treatment options include behavioral modification and clomipramine [1, 9] (Table 21.1).

Diffuse Hair Loss

1. *Telogen Effluvium*. Patients experience excessive hair shedding over the entire scalp:
   - Often preceded by a physical or emotional stressor approximately 3 months prior to the start of the hair loss.
   - Acute telogen effluvium, <3-months duration; chronic telogen effluvium, >6-months duration.
   - Causes include severe infections, postsurgical, postpartum, hypothyroidism, anemia, malnutrition, and drugs (especially beta-blockers) [10].
   - In many instances, a discernible precipitating cause cannot be found. Chronic telogen effluvium may be a precursor to patterned hair loss.
2. *Anagen Effluvium*. Abrupt and striking loss of hair (90% of hairs are in anagen phase):
   - It typically is caused by chemotherapy.
   - Occurs within days to weeks of initiation and is entirely reversible.
   - Hair regrowth typically occurs after a delay of 3–6 months.

Scarring Alopecia

Generally refers to all forms of alopecia in which there is permanent loss of hair follicles. Clinically, one will observe a smooth scalp with absence of follicular ostia and replacement with scar tissue. Patients may experience symptoms, including pain, itching, erythema, and burning sensations. This occurs as a result of continued inflammation that targets the follicle. Histopathologic correlation is often needed. As such, the classification scheme is typically divided into the type of inflammatory infiltrate involved: lymphocytic, neutrophilic, or mixed [2] (Fig. 21.1).

Lymphocytic

Central Centrifugal Cicatricial Alopecia (CCCA) (Fig. 21.5)

- A chronic, progressive disease with eventual spontaneous burnout.
- Alopecia centered on the crown or vertex and expands peripherally in a symmetric fashion.
- It is found almost exclusively in African Americans.
- Early and mild disease can be effectively treated. Long-acting oral tetracycline and topical corticosteroid can usually halt progression (Table 21.1).

Discoid lupus erythematosus. A form of cutaneous lupus erythematosus that occurs most commonly on the face, ears, and scalp (Fig. 21.6):

- Discoid lesions usually demonstrate erythema, epidermal atrophy, and dilated, plugged follicular ostia.
- Central hypopigmentation with peripheral hyperpigmentation is evident in dark-skinned individuals.
- Patients typically do not have systemic disease.
- Diagnosis requires biopsy.

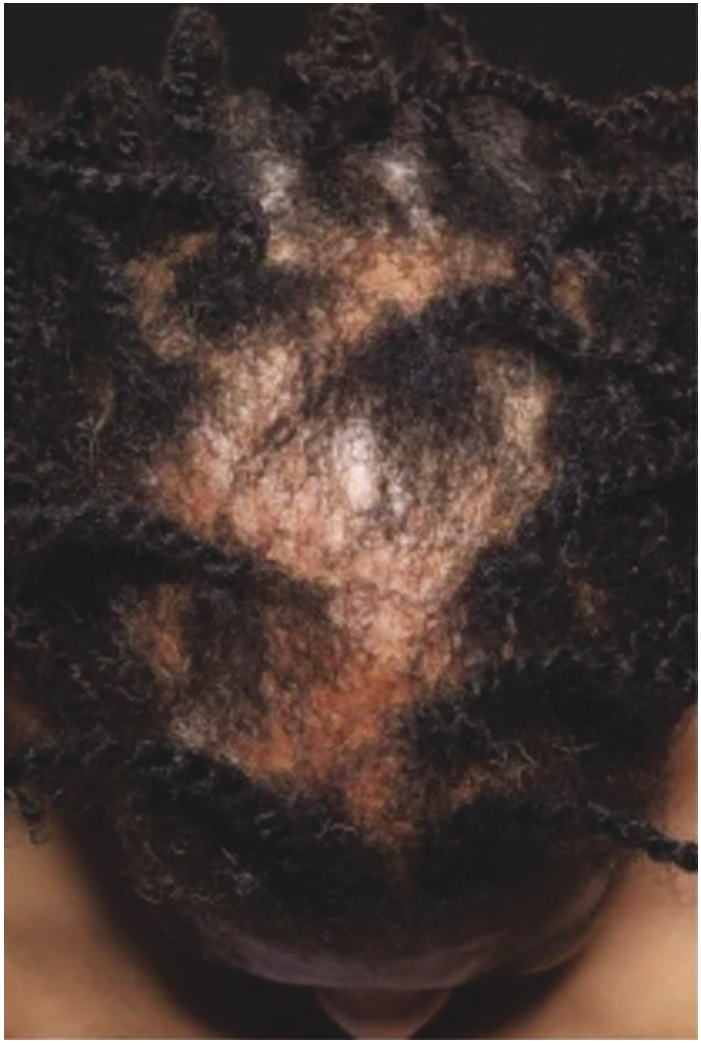

FIGURE 21.5 Central centrifugal cicatricial alopecia. Characteristic central scarring alopecia that will eventually expand centrifugally [11]

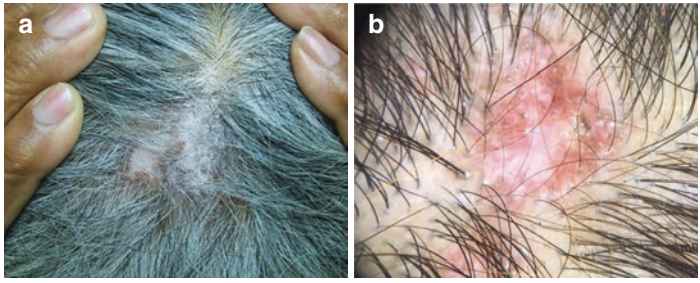

FIGURE 21.6 (**a**) Figure A demonstrates a fibrotic plaque with peripheral hyperpigmentation and central hypopigmentation, which are classic findings in the scarring alopecia of discoid lupus. (**b**) Enhanced view of a scarring alopecic plaque of discoid lupus showing loss of hair follicles centrally, follicular keratotic plugging, and central hypopigmentation with peripheral hyperpigmentation [12]

Mixed Neutrophilic and Lymphocytic

Acne Keloidalis

- Presents with small, firm papules and pustules on the occipital scalp and posterior neck.
- Usually affects young African American men and occasionally women and rarely will be seen in Caucasians.
- Often seen in conjunction with CCCA, but the cause remains uncertain.

Neutrophilic

*Dissecting cellulitis***.** Involves multiple, firm scalp nodules most often on the mid-posterior vertex and upper occiput:

- A part of the "follicular occlusion triad."[1]
- It most often affects young adult black men.
- Over time, the nodules become boggy, fluctuant, and interconnected and will discharge purulent material.

[1] Group of disorders in which the hair follicle becomes blocked with keratin, including hidradenitis suppurativa, acne conglobata, and dissecting cellulitis.

Key History and Physical Exam

Various diagnostic tools can help differentiate types of alopecia. A detailed history and physical examination will point to the diagnosis of most non-scarring and some scarring alopecias, though a skin biopsy may be required.

History

- Description: duration (acute vs. chronic), location, degree of hair loss, distribution (diffuse vs. patchy), symptoms including pruritus, redness, pain, or infection.
- Hair practices: tight ponytails, braids, weaves, use of "hot combs," chemical treatment.
- Recent changes to medications; chemotherapeutic agents.
- Medical problems: recent illnesses or surgeries, pregnancy, thyroid disorder, iron deficiency, autoimmune disorders, malnutrition.
- Emotional or psychological stressors.
- Family history.

Physical Exam

1. Gross inspection of hair:
   (a) Generalized, patterned, or focal hair loss.
   (b) Density of hair, presence of broken hairs, vellus (thin, downy premature hair) vs. terminal hairs (thick, strong mature hair).
2. Inspection of scalp:
   (a) Absence of follicular ostia and scar tissue: scarring alopecias.
   (b) Papules, pustules, scaling, perifollicular erythema.
3. Diagnostic procedures:
   (a) *Hair pull test* (useful for telogen effluvium) [1]:
      - Performed by grasping a small portion of hair and gently applying traction while sliding the fingers along the hair shafts.
        – Normal: 1–2 hairs removed.
        – Abnormal: ≥6 hairs.

(b) *Direct microscopic inspections of hair shaft* [1]:
- Exclamation point hairs: distal end broader than proximal end; seen in alopecia areata.
- Anagen hairs: elongated, distorted bulb with attached outer root sheath.
- Telogen hair: club-shaped bulb.

(c) "*Hair growth window*" (useful for trichotillomania):
- Repeatedly (weekly) shaving a small area of involved scalp to demonstrate normal regrowth.

(d) *Scalp biopsy* (useful for scarring alopecias) [1]:

4. Laboratory testing (useful for androgenetic alopecia, females particularly):
   (a) Total and free testosterone and dehydroepiandrosterone sulfate.

Treatment (Table 21.1) [1–4, 6, 8–10]

General Measures
- Treat underlying medical problems: thyroid disorder or iron deficiency.
- Discontinue any possible contributing medications, especially in telogen effluvium.
- Advise patient of importance of changing hair practices: traction alopecia or CCCA.
- Psychological intervention may be needed for trichotillomania.

Clinical Pearls
- A thorough history and physical examination of the hair and scalp are key to determining the type of alopecia.
- Treat underlying medical conditions and remove any potentially exacerbating medications.
- A change in hair practices, especially in African American women, is often necessary.
- Check nails for pitting in alopecia areata and check the ears for signs of discoid lupus.

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Part VI
Orthopaedic

Chapter 22
Knee Pain

Mitsuyo Kinjo

Introduction

The knee is the largest articular surface of any joint in the body. By convention, musculoskeletal pain lasting less than 6 weeks is defined as acute, whereas pain lasting longer than 6 weeks is chronic.

Important elements of the history are whether acute knee pain began following recent trauma or overuse during regular activity and if the pain increases with activity. If the pain developed after trauma, the presentation is likely caused by the specific activity or traumatic injury.

Key H&P

First, ask patients if the knee pain is acute or chronic. A detailed history should be asked to assess if acute knee pain developed following recent trauma or overuse. If the knee pain is unrelated to acute trauma or overuse during regular

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activity, ask if the knee pain occurs with activity. The patient is then instructed to pinpoint the location of the pain. If the knee pain is not related to activity, ask if any systemic symptoms or signs are present.

History

Knee pain is the tenth most common complaint in the ambulatory setting [1]. Knee pain is classified as acute or chronic. Acute joint pain is defined as knee pain lasting less than 6 weeks.

- Did pain develop following an injury or increasing activity level?
- Did the knee pop at the time of injury? (ligamentous tear or fracture).
- Did you twist the knee while you were sustaining the knee flexed? (meniscus tear).
- Is the pain exacerbated by activity? Does the knee feel stiff?
- Is the pain with activity worse while walking on uneven surface, walking up and down stairs, movements requiring knee flexion, or pivoting? (ligaments or meniscus tear).
- In which anatomic quadrant of the knee is the pain located? Can you point where the pain is with one finger (anterior, lateral, medial, or posterior)?
- Is the knee pain intermittent or constant?
- Is the knee pain worse after exercise?
- Do you feel the knee is getting stuck in place? Does the knee give way during walking or climbing stairs without pain preceding the episode?
- Are there any symptoms or signs of systemic illness? Is there any fever, chills, night sweats, weight loss, fatigue, or rash?
- Do you have morning stiffness? Is there pain at night?
- Is there any other joint pain or swelling?

Knowing the detailed traumatic event is helpful. If the knee is twisted while in a flexed position, meniscus tear is suggested [2]. The clicking, catching, or locking of the knee and delayed onset of knee effusion are frequently appreciated in the meniscal injury. Patellofemoral pain is common among active females in the second and third decade of life. The knee pain is anterior around or under the patella and worsens with squatting, running, or prolonged sitting [3]. Pain from the degenerative osteoarthritis tends to be accompanied by stiffness and is worse with exercise or activity. Knee pain in osteoarthritis can be anteromedial or more generalized on the medial side of the tibiofemoral joint, or anterior in the patellofemoral joint [4].

Past Medical and Surgical History

Systemic conditions including rheumatic diseases, thyroid disease, hyperparathyroidism, hemochromatosis, or sarcoidosis could be causes of knee pain. Sickle cell disease increases the risk of septic arthritis and osteomyelitis. Hemophilia or other bleeding disorders can cause hemarthrosis from minor trauma. Patients should be asked regarding any old injury or surgery to the lower extremities.

History of gout or psoriasis, infections including sexually transmitted diseases such as gonorrhea, and Lyme disease should also be asked.

Medications

History of prior treatment with analgesics, nonsteroidal anti-inflammatory drugs, intra-articular injections of corticosteroids, or hyaluronic acid should be asked. Side effects of systemic glucocorticoids could be linked to avascular necrosis of the bone (AVN), especially in patients with systemic lupus erythematosus. AVN is characterized by insidious onset of unilateral or bilateral knee pain exacerbated by weight-bearing activity.

Social History

The clinician should explore the patient's history of exercise tolerance and daily activity including the use of an ambulatory assist device and walking capability.

Physical Examination

Knee is examined using a systematic approach. First compare the affected and unaffected joints. Inspection, palpation, range of motion, strength, assessment of joint stability, and special tests to detect focal conditions should be included.

When inspecting the knee, the clinician should assess gait, swelling, ecchymosis and other signs of injury, muscle atrophy, alignment, and skin changes. If the patient can execute a duck walk, the knee is free from pathology of ligament, meniscus, or joint. The alignment of the knee, whether varus (bow-legged) or valgus (knock-kneed) deformity, predisposes the patient to osteoarthritis.

Palpation of both knees includes the skin temperature, medial and lateral joint lines, bursae, and posterior knee. Joints are normally cooler than surrounding skin, and if the joint feels warm compared to the back of the hand, it indicates inflammation. If the patient can pinpoint localized pain, attention should be paid to specific structures in that location (Fig. 22.1). With the patient's knee flexed at a 90° angle, place your thumbs on the tibial tuberosity and palpate the patellar tendon. Patellar tendinitis is suspected if the patient complains of pain at the inferior pole of the patella. If there is a tenderness over the medial anterior aspect of the tibia below the knee, pes anserine bursitis is suggested [5]. Pain on the medial joint line may indicate osteoarthritis of the medial compartment, medial collateral ligament injury, or a medial meniscal tear. Lateral joint line tenderness suggests similar conditions of the medial counterpart. Focal pain at the lateral femoral condyle is indicative of iliotibial band syndrome. Diffuse tenderness along the joint line is often caused by

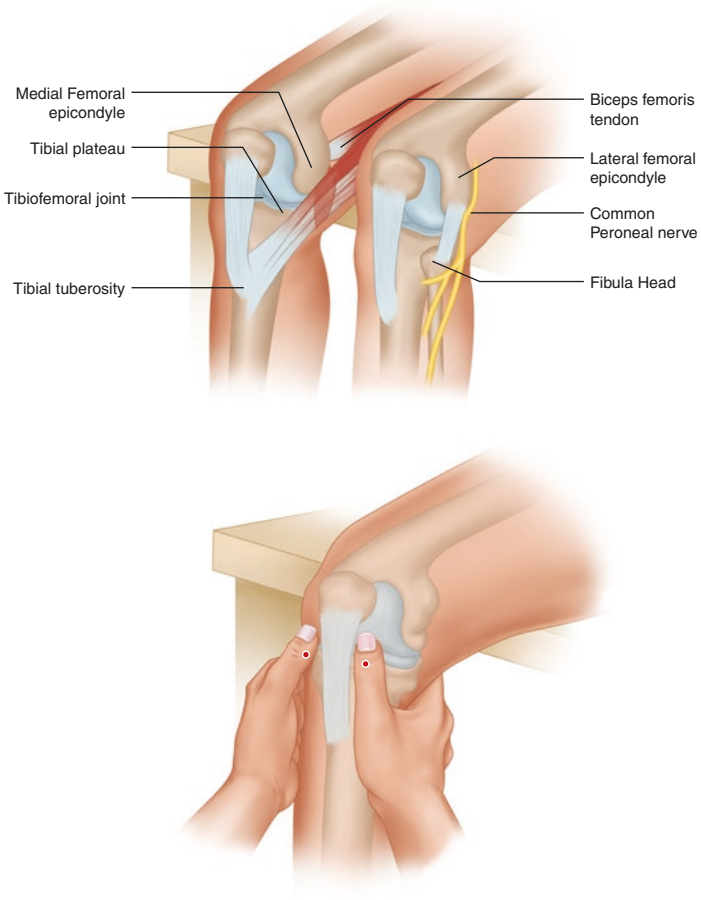

FIGURE 22.1 Anterior knee

degenerative, inflammatory, or infectious pathologies. Evaluation for a joint effusion should be determined. Effusion is seen as fullness or swelling in the suprapatellar pouch. Ballottement of the patella can confirm the knee effusion. In the case of small effusions, "milking" of the fluid from the

suprapatellar pouch to the patella and noting a parapatellar bulge can confirm effusions as small as 10 cc or less.

If the patient has diminished active but intact passive range of motion (ROM), it suggests a problem outside the joint. Common reasons are structural disruption of the muscle tendon unit, excessive pain, or motor nerve damage. Diminished ROM is often caused by a mechanical problem inside the joint such as a torn meniscus. If the patient has crepitus and retropatellar pain when the patella is being compressed during active extension, patellofemoral syndrome or patellofemoral arthritis is suggested.

Vascular assessment includes palpating the lower extremity pulses of the dorsalis pedis, posterior tibial, and popliteal arteries.

Referred pain to the popliteal space originates from the fifth lumbar (L5) nerve root and sacroiliac joint, and referred pain to the lateral aspect of the knee originates from the S1 nerve root, hip joint, trochanteric bursa, and femur.

Provocative maneuvers are only tested when initial history and examination suggest specific conditions.

The MCL valgus test is performed with knee at 0 and at 30 degrees of flexion [6]. The knee is braced by placing one hand along the lateral aspect of the knee joint and applying a valgus force to the knee while the ankle is held in a neutral position. The MCL functions as the primary restraint at both flexion angles. At 30° of knee flexion, capsule and cruciate ligaments provide no secondary restraints to valgus stress. Thus, positive valgus test at 0° suggests injury to both the MCL and cruciate ligament, but positive test at 30° suggests isolated MCL injury. Focal tenderness at the collateral ligament and opening of the joint line with this stress testing compared to the unaffected knee suggests collateral ligament injury. To perform the LCL varus stress test, place one hand along the medial aspect of the knee joint and hold the ankle, applying varus force to the knee while keeping the ankle in a neutral position.

Anterior and posterior cruciate ligament (ACL and PCL) damage can be elicited by the drawer test. With the affected

knee flexed 90°, the examiner slides the proximal tibia anteriorly (testing the ACL) or posteriorly (testing the PCL) relative to the femur, parallel to the floor. If the amount of motion is greater on the symptomatic side, the test is considered positive. Fig. 22.1 shows the anatomy of the knee and the position of the examiner's hands when doing the drawer test.

Patellofemoral pain is experienced with squatting. In the apprehension test, the quadriceps are relaxed and the knee flexed to 30°, the examiner puts pressure to the patella from the medial to the lateral side, and the patient attempts to straighten the knee as the patella is maximally displaced. Meniscus tear is suspected when joint line tenderness, abnormal smooth passive ROM, or inability to fully extend the knee is appreciated. The McMurray test is used to evaluate the menisci. The knee is flexed to the maximum pain-free position with the patient in the supine position. While externally rotating the foot, the knee is gradually extended while maintaining the tibia in external rotation. This stresses the medial meniscus and elicits a localized medial compartment click and/or pain.

The Thessaly test stimulates loading on the knee. The patient stands on one leg with his knee flexed 30° and rotates the knee and body while maintaining knee flexion. Pain or locking/catching sensation during internal and external rotation of the knee is considered a positive test.

Differential Diagnosis

See Fig. 22.2 for a visual representation of the differential diagnoses of knee pain.

Causes of acute knee pain following acute trauma or recent overuse:

- Medial or lateral collateral ligament tear.
- Anterior/posterior cruciate ligament tear.
- Meniscus tear.
- Intra-articular fracture.

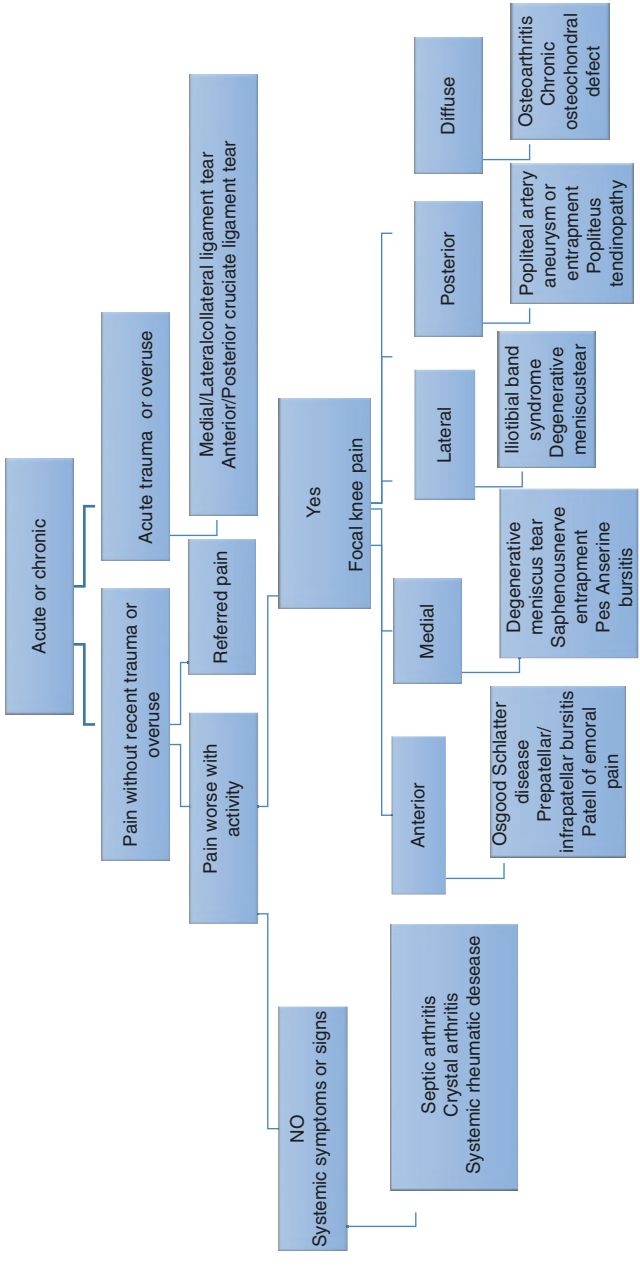

FIGURE 22.2 Differential diagnosis algorithm for knee pain

- Osteochondral defect.
- Patellar dislocation.
- Patellar tendon tear.

Knee pain associated with activity

1. *Diffuse Pain*
   - Knee osteoarthritis.
   - Chronic osteochondral defect.
2. *Anterior Knee Pain*
   - Osgood-Schlatter disease.
   - Quadriceps and patellar tendinopathy.
   - Bursitis (prepatellar and infrapatellar).
   - Plica syndrome.
   - Patellofemoral pain.
3. *Medial Knee Pain*
   - Degenerative meniscal tear.
   - Saphenous nerve entrapment.
   - Pes anserine bursitis.
4. *Lateral Knee Pain*
   - Iliotibial band syndrome.
   - Degenerative meniscus tear.
5. *Posterior Knee Pain*
   - Popliteal artery aneurysm or entrapment.
   - Popliteus tendinopathy.
   - Popliteal (Baker's) cyst.

Acute Knee Pain Not Associated with Activity

- Septic arthritis.
- Crystal-induced arthritis.
- Inflammatory arthritis (systemic rheumatic diseases).

Decision-Making

If the knee pain began following acute trauma, plain radiograph is necessary. If knee pain was unrelated to trauma but is worse with activity, magnetic resonance imaging (MRI)

may be required for the diagnosis of soft tissue knee injury such as meniscus tear or ligament problems. Ultrasound can demonstrate any knee pathology with regard to knee effusion, ligament, meniscus, and joint.

If the patient reports systemic symptoms or signs when presenting with knee pain and has local erythema, warmth, joint pain elsewhere, and an effusion, septic arthritis and crystal arthritis are in the differential diagnosis. If septic arthritis is entertained in the differential diagnosis, joint aspiration and fluid analysis including cell count with differential, gram stain, culture, and crystal analysis are warranted.

Treatment

If acute knee pain and effusion occurs immediately after trauma, the clinician should suspect injury to the collateral and anterior cruciate ligaments and the menisci and send the patient to the emergency room.

If knee pain is worse with activity but there is no inciting trauma, changing of training pattern may be required.

If atraumatic knee pain is unrelated to activity, and especially if acute knee pain and swelling are associated with constitutional symptoms along with signs of intra-articular infection by the arthrocentesis, antibiotics need be administered to treat suspected septic arthritis.

Anti-inflammatory medications are used for osteoarthritis and chronic tendon/ligament pain. For cost reasons, nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen 500 mg twice daily or ibuprofen 400–600 mg three times daily are first-line medications. These medications should be taken with food. Analgesic effects of NSAIDs are rapid, but the anti-inflammatory effects require time and repeated dosing. For this reason, it is sensible to remind patients to take these meds on a set schedule—not "as needed"—for 1–2 weeks. Relative contraindications for the use of these agents include active peptic ulcer, chronic kidney disease, and anticoagulant use. A key long-term strategy for treatment of most knee problems is weight loss.

In the treatment of knee OA, physical therapy and exercise improve flexibility and strengthen muscles around the affected joints, which leads to improvement of pain and functional outcomes. Guidelines on the treatment of knee osteoarthritis by the American Academy of Orthopedic Surgeons (AAOS) emphasizes exercise-based therapies and weight loss [7]. For degenerative medial meniscal tear without osteoarthritis, the use of physical therapy to strengthen the quadriceps muscle and lower extremity function is recommended.

Referral to an orthopedic surgeon is needed for MCL/LCL injury with knee instability, suggesting multiple ligament involvement.

Clinical Pearls

- Knee pain could be referred from a lower back or hip problem. Think of the non-knee pathology first and then evaluate the knee.
- Septic arthritis could present with absence of fever, good general health status, normal.

WBC count, or unremarkable inflammatory tests, especially in immunosuppressed patients.

Do Not Miss

Presence of crystal in the joint fluid analysis does not exclude the concurrent septic arthritis.

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Chapter 23
Shoulder Pain

Mitsuyo Kinjo

Abbreviations

AC	Acromioclavicular
NSAIDS	Nonsteroidal anti-inflammatory drugs
ROM	Range of motion

Introduction

Shoulder pain is a common complaint in the outpatient setting [1]. It can originate from intrinsic shoulder pathology or be referred from other anatomical sites. In the primary care setting, 90–95% of shoulder pain is periarticular.

The shoulder girdle is composed of three bones (clavicle, scapula, and humerus) and four articular structures (sternoclavicular, acromioclavicular, glenohumeral, and scapulothoracic joints) (Fig. 23.1). The humeral head contacts with the shallow depth of the glenoid in the glenohumeral (shoulder) joint, providing great shoulder mobility but making the glenohumeral joint susceptible to instability and

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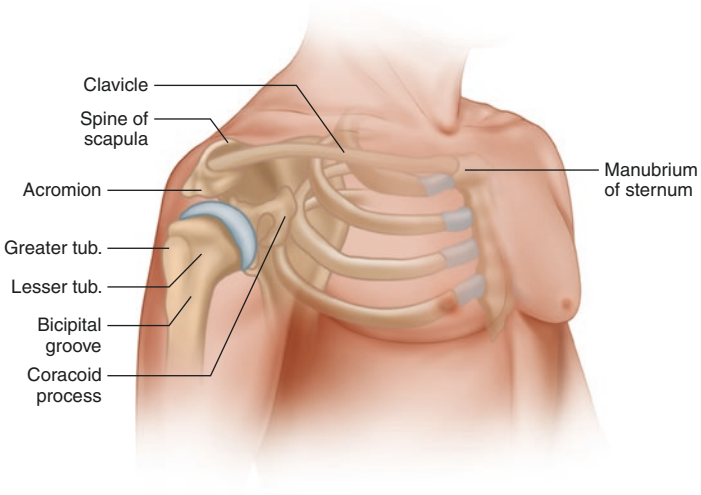

FIGURE 23.1 Anterior shoulder

injury. Rotator cuff muscles dynamically stabilize the shoulder joint. The rotator cuff is composed of four muscles (supraspinatus, infraspinatus, subscapularis, and teres minor) and forms a cuff around the head of the humerus. The supraspinatus tendon and subacromial bursa are susceptible to impingement between the greater tubercle of the humerus and the acromion.

Key H&P

First, ask patients if the shoulder pain began following an episode of trauma. Next, extrinsic and intrinsic causes of shoulder pain should be sought. Extrinsic causes include referred pain from cardiac, thoracic, or diaphragmatic pathology or radiating pain from the neck. Most of the shoulder problems seen in primary care settings are due to intrinsic shoulder disorders.

History

Once traumatic injury has been ruled out, the clinician should differentiate extrinsic and intrinsic causes. Extrinsic causes include cardiovascular, thoracic, abdominal, or neurologic conditions. Pain history and exacerbating factors, such as specific activities, need to be elicited. Shoulder pain provoked by movement, stiffness, instability, weakness, or range of motion is usually attributable to an intrinsic shoulder condition. If an intrinsic shoulder condition is suspected, the clinician should decide if the pain is due to extra-glenohumeral conditions or not. In fact, majority of painful shoulder pain stems from subacromial bursitis or supraspinatus tendinitis. The most single powerful question is to ask the patient to point to the location of pain with one finger such as the acromioclavicular joint, biceps tendon, or scapula. If the pain is at the top of the shoulder, it is either from the acromioclavicular joint or cervical radiculopathy. In acromioclavicular osteoarthritis, the pain is typically localized to the superior portion of the shoulder and is worse when reaching across the body (adduction) or in full abduction (raising the arm laterally in an arc). If the pain is at the anterior aspect of the joint, it could be radiating down from the AC joint or biceps tendinitis. In biceps tendinopathy, shoulder pain is often felt in the anterior aspect of the shoulder with tenderness in the bicipital groove. If the pain is at the lateral aspect of the joint, rotator cuff tendinopathy could be present. When the sternoclavicular joint is involved, degenerative, inflammatory, or septic arthritis is considered. If extra-glenohumeral conditions are not likely, detailed physical examination can help distinguish different pathologies in the glenohumeral joint area.

Common causes of shoulder pain differ by patient age. In older individuals, frozen shoulder (adhesive capsulitis) or osteoarthritis causes unilateral shoulder pain. Adhesive capsulitis is suspected when patients complain of pain and stiffness, progressive inability to reach overhead, and globally restricted ROM (range of motion) in any direction [2]. The patient may have a history of diabetes or prolonged immobil-

ity secondary to shoulder injury or stroke. Glenohumeral osteoarthritis may be suspected if patients complain of pain on movement in all planes, accompanied by crepitus. Acute or subacute onset of bilateral shoulder pain at rest and stiffness worse in the early morning suggests polymyalgia rheumatica. Milwaukee shoulder is characterized by a large shoulder effusion associated with hydroxyapatite crystals, typically seen in elderly women.

Middle-aged and older patients often develop rotator cuff tendinopathy. Subacromial bursitis and supraspinatus tendinitis or impingement syndrome is suspected when patients complain of subacute lateral shoulder pain worse with movement overhead. Patients typically describe a dull subdeltoid pain that can radiate down the lateral arm. It can be nocturnal pain especially when lying on the side of the shoulder. Calcific tendinitis is in the differential for subacromial conditions. It represents basic calcium phosphate deposition in the rotator cuff tendon or subacromial bursa. It is more common in the 30–50 age range and results from repetitive use or impingement. Rotator cuff tear is often of sudden onset associated with weakness and pain at night [3]. It results from impingement and tendon degeneration in older adults, while younger patients develop tear from trauma or repetitive use. Inflammatory polyarthritis involving the hands and wrists suggests rheumatoid arthritis. If inflammatory spinal pain is associated with extra-articular features such as uveitis, psoriasis, or inflammatory bowel disease, spondyloarthritis is suspected. In younger adults, sports injury including subluxation of the shoulder joint and sprain of the acromioclavicular joint are common. Superior labrum tear is suspected in patients with throwing or overhead activities, and the pain is greatest with the shoulder abducted and externally rotated.

Past Medical and Surgical History

Ask about previous injuries, treatments, and comorbidities such as diabetes.

- Did the shoulder pain develop following traumatic injury or overuse?
- Is there is a history of cardiac disease? Does the shoulder pain develop with chest pain on exertion?
- Is there presence of fever, weight loss, dyspnea, or chest pain?
- Does the shoulder pain and/or numbness develop when you move the neck to the side?
- Is there any history of prior shoulder pain?
- Where is the site of the shoulder pain? Is it localized or diffuse? Is it in the anterior, lateral, or posterior aspect of the shoulder?
- Was the onset of shoulder pain sudden or gradual?
- Was the duration of shoulder pain acute (< 6 weeks), subacute (6–12 weeks), or chronic (>6 weeks)?
- Does the pain in the anterior shoulder get worse when reaching overhead? (rotator cuff tendinopathy).
- Is there stiffness and difficulty moving the shoulder when reaching overhead?
- Is the shoulder pain aggravated when moving in multiple directions?
- Does the head of the biceps hurt when lifting or carrying heavy objects?
- Is the shoulder pain at rest and is it worse in the morning?
- Is there weakness? Any radicular pain related to the shoulder pain?

Physical Examination

First, compare the affected and unaffected joints. Inspection, palpation, range of motion, strength, assessment of joint stability, and special tests to detect focal conditions should be included.

Inspect symmetry, bulk, deformities, and atrophy above and below the scapular spine. Muscle atrophy below the

scapular spine in an older patient suggests chronic rotator cuff tear or suprascapular nerve injury [3]. Ask the patient to raise the arms in a push-up position with both hands against a wall and view scapular position from behind. An elevated protracted scapula described as winging suggests dysfunction of the long thoracic nerve or muscular dysfunction.

Full range of motion suggests a normal glenohumeral joint, rotator cuff tendons, and muscles. Have the patient perform six different shoulder motions including abduction, adduction, flexion, extension, and internal and external rotation. Internal and external rotation should be tested with the shoulder abducted to 90°. For abduction, ask the patient to raise the arm from his/her side to overhead (0–180°). If the patient has limited active ROM, evaluate passive ROM with assistance to raise the arm until limited by pain. Active ROM is easily tested with the "Apley scratch test," which can be used to provide useful information on shoulder range of motion. First, ask the patient to touch the superior medial tip of the opposite scapula to assess external rotation and abduction. Then ask the patient to reach behind the back and touch the tip of the inferior scapula on the opposite side to assess internal rotation and adduction (Fig. 23.2). Finally, ask the patient to reach across the chest and touch the opposite shoulder to assess adduction.

When palpating the shoulder and surrounding pathology, examine the cervical spine first and then move from proximal to distal structures: sternoclavicular joint, clavicle, scapular spine and adjacent musculature, acromion, subacromial space, acromioclavicular joint, bicipital groove, and greater and lesser tuberosity of the humerus.

Provocative maneuvers for examination of rotator cuff injury are important. The supraspinatus tendon is susceptible to subacromial impingement. Several maneuvers can assess rotator cuff injury. Supraspinatus isometric strength is examined by having the patient abduct the arm to 30° (deltoid muscle initiates abduction) and have him/her resist continuous pressure while the examiner attempts to adduct the arm. A painful arc test is to simply have the patient actively abduct the arm in the

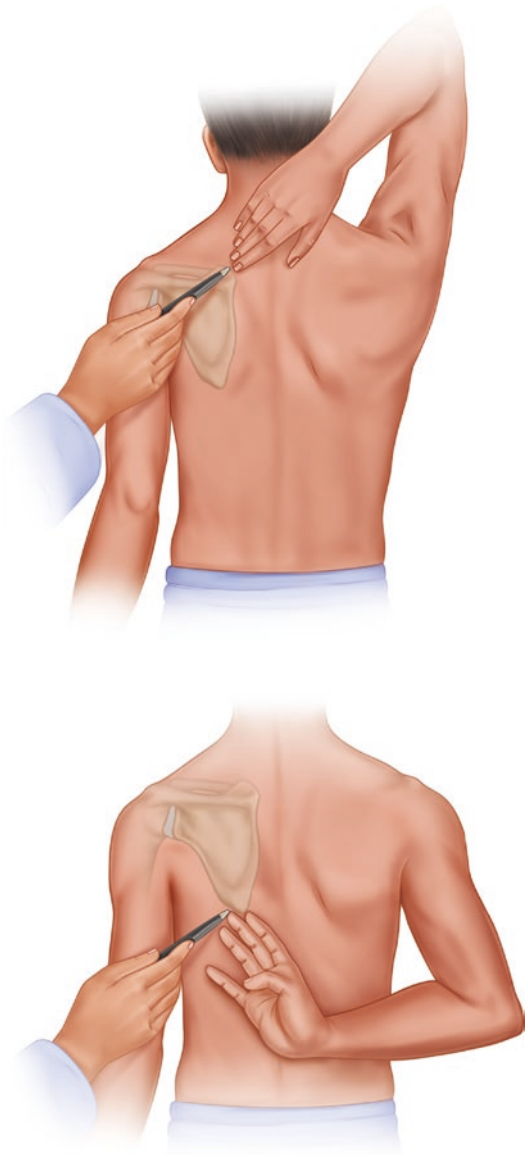

FIGURE 23.2 Apley scratch test

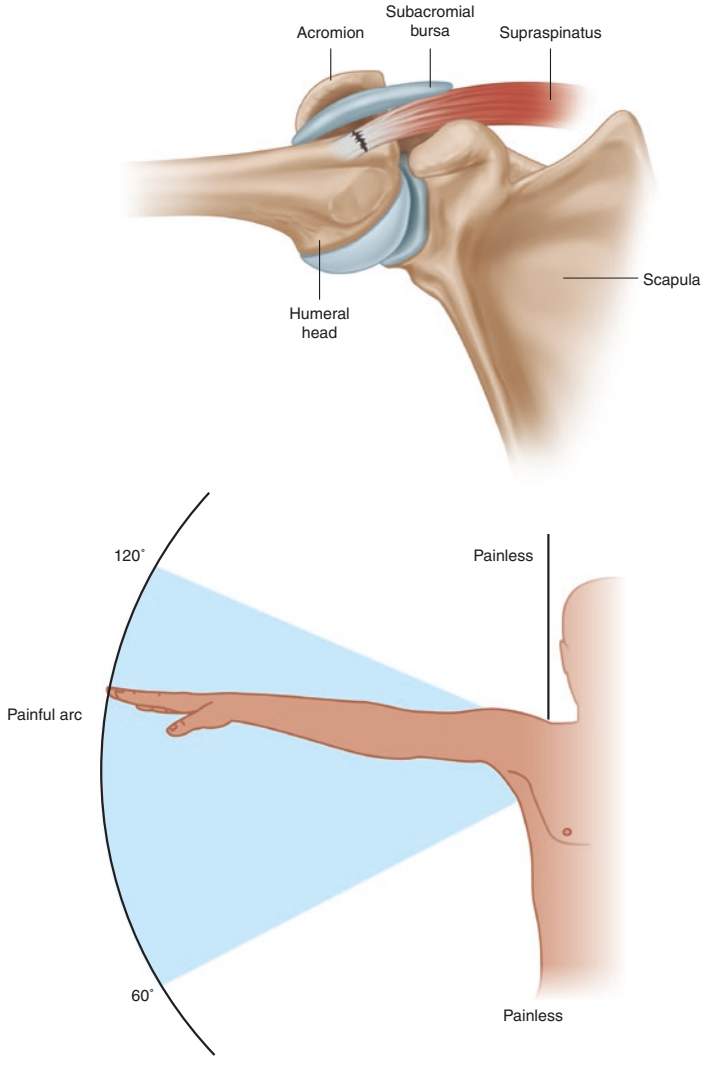

Figure 23.3 Impingement sign

scapular plane (Fig. 23.3). The test is positive when the pain is provoked with active abduction between 60° and 120° [4]. This is one of the most helpful physical examination tests for sub-

acromial impingement (supraspinatus tendinopathy or subacromial bursitis) [3]. Pain between 120° and 180° suggests problems in the acromioclavicular joint. Rotator cuff complete tear is confirmed by a positive drop arm test. The examiner abducts the patient's arm while supporting it at the elbow and then observes to see if the patient can maintain the arm position after the examiner removes the support. Partial rotator cuff tear is difficult to distinguish from supraspinatus tendinitis. Findings persist after subacromial lidocaine injection.

Patients with adhesive capsulitis or glenohumeral arthritis have diminished active and passive ROM in any direction. Acromioclavicular (AC) joint disease is suspected if localized pain over the AC joint, pain on abduction, or pain on cross arm adduction is present. Biceps tendinitis related to degenerative changes is common in older patients. In order to accurately palpate the biceps tendon, the clinician first identifies the greater tubercle of the humerus and moves his/her fingers medially into the bicipital groove and then rolls the biceps tendon under his or her fingers as the shoulder is rotated internally and externally. Special maneuvers for biceps injury include Yergason's test (Fig. 23.4). In this test, the patient

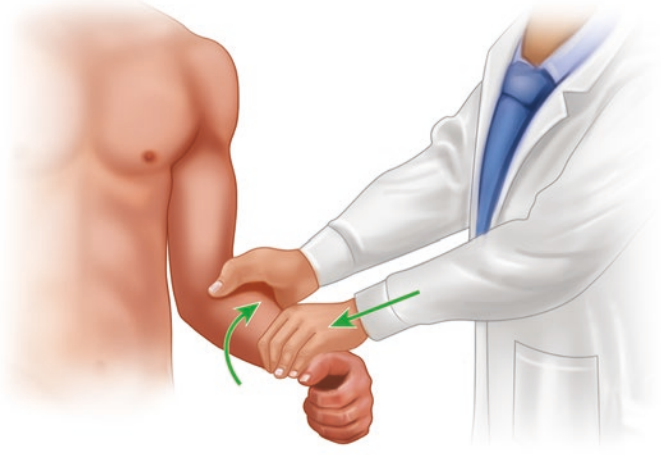

Figure 23.4 Yergason's test(bicipital tendinitis)

flexes the elbow to 90° and the clinician provides resistance to forearm supination. If pain in the area of the bicipital groove is reproduced, the test is positive. Isolated biceps tendinitis is uncommon and most often is seen with subacromial disease.

Differential Diagnosis

Please see algorithm (Fig. 23.5) for a visual depiction of the differential diagnosis of shoulder pain.

Pain from surrounding structures
- Cervical spine disease or spinal cord lesion affecting nerve root compression (C5, C6).
- Suprascapular nerve compression.
- Thoracic outlet syndrome.
- Brachial plexus lesions (brachial plexopathy).
- Herpes zoster.

Abdominal
- Hepatobiliary disease.
- Diaphragmatic irritation (liver abscess, ruptured ectopic pregnancy, splenic injury).

Cardiovascular
- Myocardial ischemia.

Thoracic
- Upper lobe pneumonia.
- Apical lung tumor.
- Pulmonary embolism.

Intrinsic Shoulder Pain

Nonspecific shoulder pain
- Polymyalgia rheumatica.

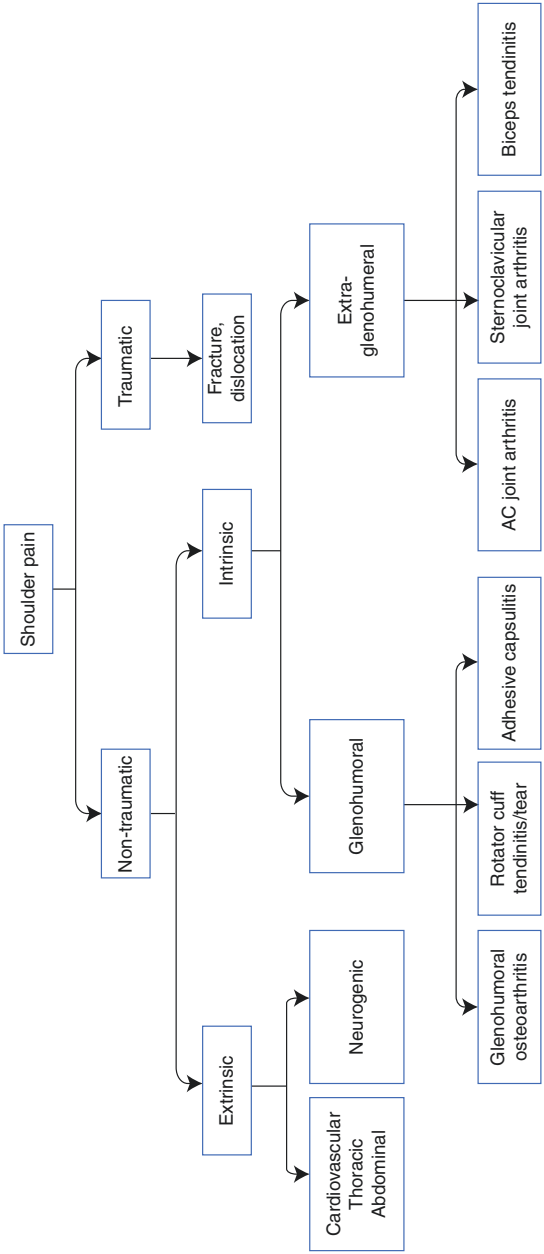

FIGURE 23.5 Shoulder pain algorithm

Lateral shoulder pain
- Rotator cuff injury (impingement syndrome, tendinopathy, partial thickness or full thickness tendon tear).
- Adhesive capsulitis.
- Cervical radiculopathy.
- Labral tear.
- Proximal humeral fracture.

Anterior shoulder pain
- Rotator cuff disease.
- Glenohumeral osteoarthritis.
- Acromioclavicular arthritis.
- Acromioclavicular separation.
- Biceps tendinitis/rupture.
- Proximal humeral fracture.
- Labral tear.

Posterior shoulder pain
- Scapular instability.
- Scapulothoracic bursitis.
- Cervical radiculopathy.
- Subscapular nerve entrapment.

Decision-Making

Poorly localized shoulder pain is often referred from internal pathology, including cardiac ischemia. Cervical nerve root pain is usually sharp in nature radiating from the neck to the posterior shoulder and arm.

If a traumatic injury is present based on the patient's history, shoulder X-ray should be performed. Blunt trauma could cause fractures of the clavicle or proximal humerus, dislocation of the glenohumeral joint, and sprains/separation of the AC joint. If the patient has limited ROM with severe shoulder pain with or without trauma, plain shoulder X-ray is recommended to assess arthritis of the glenohumeral joint,

acromioclavicular joint, or sternoclavicular joint. In osteoarthritis, characteristic X-ray changes include cartilage loss, subchondral sclerosis, and osteophytes. Plain X-ray is useful in identifying glenohumeral or AC osteoarthritis, calcific tendinitis, or other bone pathology. Calcium deposits in the supraspinatus tendon near its insertion may be seen.

Ultrasound can be a great aid for rheumatologic exam for tendon and articular pathology in combination with history and physical examination. MRI should be checked if labral tear or rotator cuff tear is suspected. MRI is indicated when surgery is considered for suspected rotator cuff injury, impingement, avascular necrosis, biceps tendinopathy, inflammation, and tumors.

Treatment

Treatment goals are to reduce pain and improve ROM. NSAIDs are recommended for anti-inflammatory effects. As a general rule, patients should be advised to move the shoulder in all directions at least daily to preserve ROM.

Tendinitis, Bursitis, and Arthritis

NSAIDs are the first-line therapy for these common disorders along with avoiding any repetitive motions that may have aggravated these structures in the first place. Medication should be prescribed on a set basis for the first 7–14 days, not as "as needed."

In patients with calcific tendinitis, ultrasound-guided needling of calcific deposits (barbotage) can be helpful. Patients unable to tolerate NSAIDs may respond to injection of steroids, as described under the adhesive capsulitis section below.

Rotator Cuff Injury

Ice can be used to reduce the acute inflammation. If the pain is initially relieved with use of ice, continue icing 20–30 min as often as every 2 h. Rest to avoid activities that aggravate symptoms (e.g., raising arm or overhead reaching). Nonsteroidal anti-inflammatory medication such as ibuprofen or naproxen is used to reduce pain and inflammation.

Stretching and range of motion exercises should be recommended either as part of a home self-management plan or a physical therapist plan.

The patient can be advised to do "pendulum stretching exercises: which can be started immediately after a shoulder injury [5]. While standing or sitting, the patient dangles his/her arm and allows the arm to slowly swing back and forth, then side to side, and then in small circles in each direction to the degree only with minimal pain. If patients do not respond to conservative measures over 3 months and complain of progressively worsening pain or weakness, clinicians should consider specialist consultation.

Adhesive Capsulitis

Physical therapy with gentle shoulder mobility exercise is first recommended. Intra-articular glucocorticoid injections early in the course of frozen shoulder may be beneficial. Combined physical therapy following intra-articular glucocorticoid injection provides faster improvement [6]. Triamcinolone 20–40 mg or methylprednisolone 20–40 mg are suitable. Surgery does not seem to improve the outcome.

Clinical Pearls

- Shoulder pain is often referred from the neck. First, think of the non-shoulder pathology especially when the description of the pain is vague or diffuse, and then evaluate the shoulder.
- Contrary to common sense, "If it hurts, don't move it" usually does not apply to shoulder pain as the risk of adhesive capsulitis increases with each day of immobility.

Do Not Miss this!

- Extrinsic causes of shoulder pain could be referred from cardiac or intra-abdominal pathology; thus, time to diagnosis is crucial.
- Pain from biceps tendinitis is quite anterior rather than lateral. Do not forget to examine this area.

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Chapter 24
Back Pain

Mitsuyo Kinjo

Introduction

Majority of patients who present with back pain in the primary care setting will have nonspecific back pain [1]. Acute back pain less than 4 weeks' duration is usually self-limited, but rare cases may reflect serious systemic etiology. It is important to look for evidence of specific etiology of back pain. History of back pain include location, duration, and severity of the pain and activities or detailed events prior to back pain. In order to make sure not to miss serious etiology, red flag signs and symptoms should be asked.

Upper/mid back pain indicates pain in the posterior neck to the lowest rib edge, and low back pain refers to pain in the thoracolumbar spine down to the sacrum. Upper/mid back pain are often due to mechanical problems, whereas low back pain is related to various pathologies.

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Key H&P

First, we ask patients if the back pain was acute/sudden or chronic. Patients with severe back pain with abrupt onset or abnormal vital sign should be seen in the emergency room.

Next, red flag signs reflecting underlying systemic illness or acute condition requiring urgent intervention should be sought in the history. Clinicians should be alert to clinical pictures of back pain resulting from cancer, infection, fracture, or ankylosing spondylitis. Constitutional symptoms including unintentional weight loss or night sweats, history of malignancy, neurologic symptoms such as weakness or gait instability, numbness/sensory changes, bowel/bladder symptoms, history of recent bacterial infections, prolonged glucocorticoid use, and recent history of procedures in the back should be asked.

Distribution of low back pain is classified as either axial (pain generally localized to the low back) or radicular neuropathic (pain radiating to the lower extremities). This classification often helps primary care physician to identify disease process occurring in the lumbar spine [2].

History

Abrupt-onset, extremely sharp back pain causing patients to seek medical attention within hours of the onset may suggest vascular etiology. Spinal cord infarction secondary to aortic dissection leading to the anterior spinal artery may present with concomitant severe back pain and flaccid paralysis.

Epidural spinal cord compression and cauda equina syndrome are serious neurologic conditions. Spinal cord at the L1–L2 level connects to the cauda equina, in which autonomic nerve ends and lumbosacral nerve roots float in cerebrospinal fluid. Compression and damage to the spinal cord or cauda equina could lead to potentially irreversible loss of function of the lumber plexus below the conus medullaris of the spinal cord. Sudden onset of severe back pain

radiating to both legs associated with saddle anesthesia and urinary retention (S3–5 nerve roots) suggests cauda equina syndrome. Weakness of plantar flexion of the feet and loss of ankle jerks suggest S1–2 nerve root involvement. Numbness and cold or burning sensation of the lower extremities in the affected nerve roots are also common. This rare but serious conditions usually arise from similar etiologies to that of spinal cord compression due to trauma, tumors (intradural extramedullary tumor, epidural tumor), massive midline intervertebral disc herniation, spinal stenosis, epidural abscess, or inflammatory diseases (e.g., spondyloarthritis, sarcoidosis) [3].

Osteoporotic fracture commonly affects the thoracolumbar junction (T12–L1) and may result in significant back pain. Acute back pain may develop after sudden lifting or bending and is variable in quality.

Inflammatory back pain is a key feature of spondyloarthritis. Inflammatory back pain includes at least four of the following five features: insidious onset, age of onset before 40 years, improvement with exercise, no improvement with rest, and pain at night [4].

When serious causes of back pain are not likely, differential diagnosis of axial low back pain or radicular pain in the primary care setting includes intervertebral disc herniation, spinal stenosis, facet joint osteoarthritis, sacroiliac joint inflammation, and paraspinal musculature spasm.

Intervertebral disc herniation tends to develop in patients younger than 45 years old, the onset of which is usually insidious but may involve an inciting event such as lifting or bending. Patients will often report localized pain to the midline of the spine [5]. Herniated intervertebral disc at the L4–L5 or L5–S1 is also an important cause of radicular pain. Clinicians should ask the distribution of the pain, which should follow one or multiple dermatomal pattern and is worsened by forward bending, coughing, or sneezing and improved with recumbency.

Lumbar facet joint hypertrophy frequently often occurs in patients over 65 years old. Low back pain may be localized to

the paraspinal region, which is worse with standing and better with sitting or recumbency [5].

Sacroiliac joint pain is usually reported as postural low back pain of the paraspinal region below L5 or gluteal pain that worsens in a sitting position radiating to the thigh or distal to the knee and is worsened by transitional movements such as rising from a sitting position. Clinician needs to rule out piriformis muscle pain which presents with unilateral or bilateral buttock pain radiating to the L5 or S1 dermatome distribution [6]. Physical examination with negative straight leg raising test in piriformis muscle syndrome is helpful to distinguish from radicular pain.

Lumbar spinal stenosis could present with both midline back pain and radicular pain. Patients aged greater than 65 years should be asked about neurogenic claudication, in which prolonged standing and walking worsen the pain and sitting and stooping or bending forward improve the pain. Bilateral buttock or leg pain is also important [7]. Neurogenic claudication is considered to be caused by congestion and hypertension around the nerve root.

Axial low back pain in adolescents and young adults often originates from spondylolysis caused by bilateral stress fractures of the pars interarticularis of the L5 vertebra [8]. This pain is worsened by repetitive flexion-extension movements of the lumbar spine.

Specific underlying pathology or condition cannot be identified for the vast majority of patients. Most patients with nonspecific back pain improves within a few weeks.

Past Medical and Surgical History

Epidural abscess or vertebral osteomyelitis could be caused by hematogenous spread from recent bacteremia or contiguous spread from adjacent tissue, or direct inoculation from spinal surgery. Insidious onset of spinal pain exacerbated by physical activity with or without fever progressively worsens over several weeks. Epidural abscess may cause

shooting pain in the affected nerve root, which may progress to motor weakness or bladder/bowel dysfunction. High index of suspicion is the key for the diagnosis especially for those with risk factors such as diabetes, alcoholism, hemodialysis, IV drug user, HIV, or spinal surgery/epidural catheter.

History of cancer and severe back pain at rest suggest metastatic skeletal lesion. The breast, prostate, lung, thyroid, kidney, and gastrointestinal tract have propensity for skeletal metastasis.

Neoplastic epidural spinal cord compression arises in the thoracic spine (60%), lumbar spine (30%), and cervical spine (10%).

Previous spinal surgeries or history of osteoporosis or prior fractures should be asked.

Medications

Prolonged corticosteroid use increases the risk of vertebral compression fracture. Risk of infection is increased with immunosuppressant use.

Social History

Physical demands of work in manual workers influence the higher prevalence of low back pain compared to sedentary occupation [9]. Lower educational status and obesity are also related to increased risk of low back pain [10].

- Where is the pain in the back? Could you point where the pain is located?
- Is there pain radiating to your buttock or legs?
- How severe is the pain? Have you had any back pain before? Is the current pain better or worse than the previous back pain?
- Do you have prior history of cancer? If so, how long ago was it?
- Do you have fever or weight loss?

- Do you find it difficult to walk? Is there any numbness or change in sensation?
- Do you have any fecal/urinary incontinence?
- Do you have any recent preceding infection (bacterial pneumonia or urinary tract infection)?
- Does the pain wake you up at night?
- Is the back pain worse at rest or during the night? Does the pain get better when you walk? (spondyloarthritis).
- Is the pain localized to the back or radiating to the buttock or legs?
- Is the pain worse by bending forward, coughing, or prolonged sitting? Is the pain improved with recumbency?

Physical Examination

A complete neurologic examination should be performed especially when red flags or neurologic complaints are present. Weakness of the lower extremity or bowel/bladder dysfunction could be due to a cervical spinal cord compression if subtle examination findings in the upper extremities such as hyperreflexia or a positive Hofmann sign are found.

In patients with sciatica or pseudoclaudication, the straight leg raising test and crossed straight leg raising test (a leg elevation of less than 60° with pain radiating below the knee is positive) could illicit radicular pain by compression or irritation of the L4–S1 nerve roots, but sensitivity is generally low [11]. Impaired reflexes of the Achilles tendon (S1 radiculopathy) or patellar tendon (L4 radiculopathy), weakness of ankle dorsiflexion or extension of the great toe (L5 radiculopathy), and reduced sensation of dermatomal distribution are also helpful (Fig. 24.1). The L5 and S1 nerve roots are mostly involved in lumbar disc herniation.

In lumbar spinal stenosis, motor or sensory findings mostly reflect the involvement of proprioceptive fibers in the posterior columns of the spinal cord [12]. The Romberg sign and wide-based gait have moderate sensitivity but high specificity.

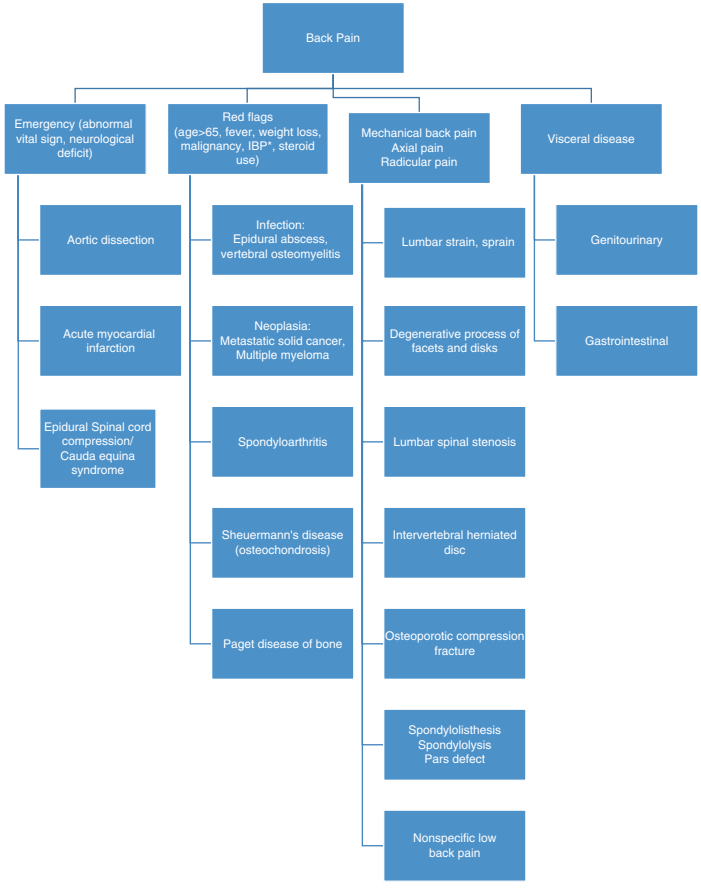

FIGURE 24.1 Backpain algorithm. *IBP: inflammatory back pain

Lumbar spinal pain is diminished on lumbar flexion, and vibratory and pinprick sensation are reduced. Achilles tendon reflex is absent [13]. Sacroiliac joint pain is likely if it is reproduced by three or more of the following physical examinations: compression of the iliac crest in the lateral position, downward pressure on the anterior superior iliac crest;

FABER test (flexion abduction external rotation of the thigh and hip), Gaenslen test (hyperextension of the leg on the affected side), and Fortin finger test (pain localized on fingerbreadth of the posterior iliac crest) [14].

Differential Diagnosis

Serious conditions requiring emergent evaluation:
- Aortic dissection.
- Acute myocardial infarction.
- Anterior spinal artery syndrome.
- Epidural spinal cord compression.
- Cauda equina syndrome: trauma, tumors and metastatic lesions, spinal stenosis, inflammatory diseases (e.g., spondyloarthritis), and infectious conditions (e.g., tuberculosis).

Medical conditions requiring nonemergent evaluation:
- Spinal epidural abscess or vertebral osteomyelitis.
- Metastatic solid cancer or multiple myeloma.
- Spondyloarthritis.

Mechanical back pain:
- Vertebral compression fracture.
- Lumbar spinal stenosis.
- Intervertebral herniated disc.
- Spondylolisthesis.
- Lumbar spondylolysis.
- Nonspecific low back pain.

Decision-Making

Plain radiography should be limited to patients with signs or symptoms suggesting systemic diseases.

Immediate imaging with MRI is indicated when progressive motor weakness, new urinary retention, and saddle anesthesia suggest cauda equina syndrome. If current or recent cancer history or high clinical suspicion for malignancy is

present, either MRI or plain X-ray will be checked. Spinal infection (epidural abscess or osteomyelitis) is strongly suspected with risk factors including history of IVDU, recent infection, hemodialysis, or immunosuppressive agent use. MRI and inflammatory signs with ESR or CRP need to be checked. If blood cultures are positive for monogenic, likely pathogen (e.g., *Staphylococcus aureus*), biopsy of the infected vertebral bone or intervertebral disc may not be necessary.

If vertebral compression fracture is suspected with advanced age, trauma, history of prolonged glucocorticoid use, or prior osteoporotic fracture, plain X-ray film should be checked. Compression fracture with hypercalcemia, anemia, or elevated creatinine at presentation could be key features to suspect multiple myeloma. Monoclonal (M) protein can be detected by protein electrophoresis of the serum (SPEP) and/or of urine (UPEP) from a 24-h collection along with immunofixation of the serum and urine.

When spondyloarthritis is suspected, HLA-B27 positivity and MRI of the sacroiliac joints help diagnose this condition.

Early imaging of axial low back pain or radiculopathy should be deferred until after initial treatment when a patient has weaker risk factors for cancer or vertebral compression fracture. No imaging is indicated when back pain has improved or resolved 1 month after treatment, or the patient's clinical status does not change even with previous imaging [15].

Treatment

Patients with acute low back pain should be advised against bed rest and encouraged to return to daily living and activities.

Pharmacotherapy

Most acute low back pain will resolve within 8 weeks without active treatment. Evidence supports the use of nonsteroidal anti-inflammatory drugs (NSAIDs) up to 3 months of chronic

axial low back pain. Short-term treatment within 4 weeks' duration is recommended—ibuprofen 400–600 mg four times daily or naproxen 250–500 mg twice daily and taper as tolerated. Recent evidence concluded that acetaminophen showed no benefit compared to placebo in acute low back pain [16]; thus, only selected patients with contraindication to NSAIDs can be recommended for the use of acetaminophen.

Non-benzodiazepine muscle relaxants may be effective in patients with acute low back pain who are refractory to initial pharmacotherapy [17]. Cyclobenzaprine is a reasonable choice. Benzodiazepine muscle relaxant should not be used due to physical dependence. Tramadol may be effective for acute and chronic low back pain [18]. For radicular pain, gabapentinoid could be used as add-on analgesics or stand-alone therapy.

In chronic axial pain, the use of simple analgesics such as acetaminophen or tramadol in combination with an antidepressant appears to be efficacious [19]. Tricyclic antidepressants or duloxetine can be tried if chronic low back pain is refractory.

Non-pharmacotherapy

Patients with acute low back pain should be advised against bed rest. We encourage patients returning to activities or work as soon as possible. In patients with acute low back pain, exercise does not improve outcomes. For patients with subacute (4–12 weeks) or chronic (12 weeks or longer) nonspecific low back pain, exercise should be encouraged for those who were already active. Referral to physical therapy to strengthen abdominal muscle by increasing lumbar flexion and reducing lumbar lordosis may prevent recurrence of low back pain. Aerobic exercise is recommended to all patients for chronic back pain.

Clinical Pearls

- Only a small proportion of patients with inflammatory back pain will have spondyloarthritis. Not all patients with spondyloarthritis have inflammatory back pain.

- Osteoporotic compression fracture should not guide you away from malignancy-related vertebral compression fracture. Always look for any signs of malignancy or infection even when the history is highly suggestive of osteoporotic fracture.

Do Not Miss

- Cauda equina syndrome secondary to malignancy or midline intervertebral disc herniation should not be missed as it could become irreversible in neurological deficit.
- Aortic dissection and anterior spinal artery infarction are life-threatening conditions.

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Part VII
Neurologic

Chapter 25
Dizziness

Robert Kennedy Jr

Introduction

A dizzy patient presenting to a busy clinician poses a unique diagnostic challenge. Fortunately, a focused, structured evaluation can guide a provider through the most common differentials in order to establish a clear diagnosis and develop an effective treatment plan. It should be noted that about 5% of primary care visits deal with a chief complaint of dizziness and more than 50% of patients with dizziness seek help from their primary care clinician [1]. The causes of dizziness remain constant across a wide spectrum of practice settings [2].

Dizziness can be classified into four main categories: vertigo, presyncope, disequilibrium, and lightheadedness. Making a diagnosis can initially seem challenging due to the often vague, nonspecific, or inconsistent nature of the patients' reporting. In addition, some causes of dizziness can share similar features and precipitants. A broad differential consisting of both malignant and benign causes coupled with nonspecific patient descriptors can lead to diagnostic frustration.

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Despite these barriers, the cause of the dizziness is revealed by the patient's history in more than 50% of cases [3].

The patient's initial, raw, unguided description of their symptoms is the most important step in determining the cause of their dizziness. For this reason, it is imperative to obtain an unguided, pure description of what the patient is actually experiencing. This can be achieved by starting with open-ended, non-leading questions such as: "Without using the word 'dizzy' tell me what you are feeling" or "When you say you feel dizzy, what exactly do you mean?" After the provider has cast the net widely, wait and listen as the diagnostic clues come to the surface.

Patients with vertigo tend to report a spinning sensation or fictitious sense of motion. If such a patient also has migraine symptoms (photophobia, phonophobia, aura, or typical headache), vertiginous migraine should also be considered, affecting 3% of the population and 10% of migraineurs [1]. Patients with presyncope may report a feeling of pending loss of consciousness or "blackout." Patients with disequilibrium may report being "off-balance" and "feeling wobbly" or describe other perturbations in balance and coordination. Feelings of lightheadedness are often very vague, imprecise, and difficult for patients to articulate without using the word "dizzy." They may describe feeling disconnected from the environment, a sense of floating or giddiness; it is this abstract nature of symptom reporting that in itself is actually diagnostic. It should be noted that psychiatric causes can be identified in many of these patients as well [4] (Fig. 25.1).

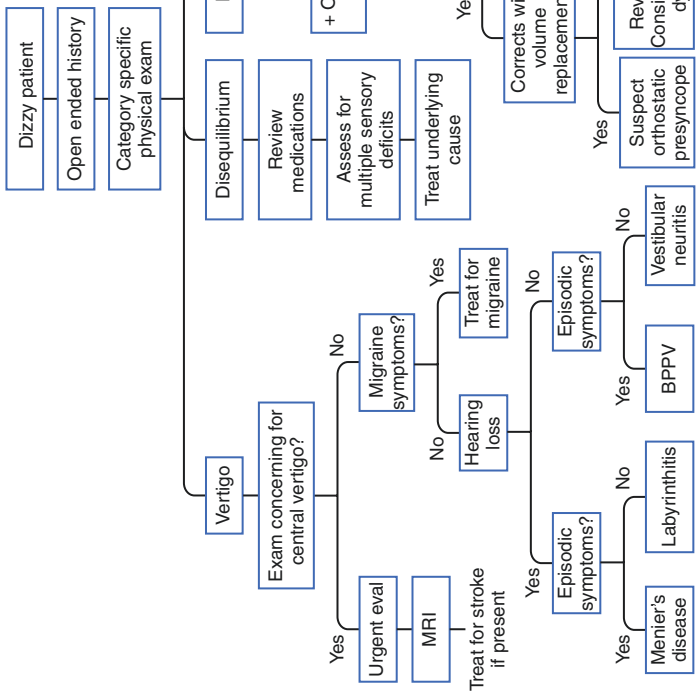

FIGURE 25.1 Approach to patient with dizziness

Decision-Making/Differential Diagnosis

Vertigo

Vestibular dysfunction accounts for more than 40% of dizzy episodes. Here the subtypes include benign paroxysmal positional vertigo (BPPV), vestibular neuritis (viral infection that involves the vestibular nerve), labyrinthitis (postinfectious inflammation of the labyrinthine organs), and Meniere's disease (increased endolymphatic fluid in the inner ear). Central vertigo (brainstem stroke, posterior circulation insufficiency) and migrainous vertigo, as previously noted, are also important diagnostic considerations. Vertigo can be caused by disturbance of the peripheral vestibular system (vestibular portion of the eighth cranial nerve and vestibular labyrinth) or by lesions within the central nervous system (brainstem or cerebellum). Nausea and vomiting are typical with acute vertigo, but can be mild or short lived in BPPV. Interestingly, peripheral vertigo tends to cause more severe nausea and vomiting than central causes. Movement worsens all types of vertigo, and even though patients with peripheral vertigo may not want to move, they are usually able to walk. In comparison, patients with central vertigo experience greater impairment in gait and posture and are often very ataxic and unable to walk [5].

Most patients have benign disorders of the peripheral vestibular system and dysfunction of either the vestibular nerve (vestibular neuritis) or the labyrinth (labyrinthitis). A few (less than 5%) may have serious strokes of the cerebellum or brainstem, which may rapidly cause coma and death from acute hydrocephalus or brainstem compression. For this reason, it is imperative to make a clinical distinction between central and peripheral vertigo [6].

Central vs. Peripheral Vertigo

Severe vertigo may occur in the setting of acute peripheral and central lesions. However, there are some clinical clues that favor a central cause over a peripheral cause. An acute vertebrobasilar stroke is almost always accompanied by other signs and symptoms of brainstem ischemia such as diplopia, dysphagia, weakness, or numbness. A history of atherosclerotic cardiovascular disease and associated risk factors should heighten a clinician's concern for vertebrobasilar ischemia. Findings on the physical exam that suggest stroke in dizzy patients include normal bilateral vestibulo-ocular reflexes (noted on head impulse test), skew deviation, (described later in the chapter), abnormal visual tracking (saccadic pursuit), and direction-changing nystagmus. Visual fixation can suppress nystagmus from the peripheral lesion but not from a central cause. In peripheral lesions, the predominant direction of nystagmus remains the same in all directions of gaze; nystagmus that changes direction with gaze shifting is suggestive of a central abnormality. Other features that suggest a peripheral cause include falling in the opposite direction to nystagmus and horizontal/torsional nystagmus. In summation, the probability of stroke is increased in the setting of severe truncal ataxia, normal vestibulo-ocular reflex, skew deviation, saccadic pursuit, direction-changing nystagmus, and nystagmus that is not suppressed with visual fixation (see Table 25.1) [5].

Table 25.1 Findings concerning for central vertigo

Severe ataxia
Direction-changing nystagmus
Nystagmus not affected by fixation
Saccadic pursuit
Skew deviation
Nystagmus does not fatigue with repeated dix-Hallpike maneuver

BPPV

BPPV is the most common form of peripheral vertigo and tends to occur when the patient moves the head in a particular position as in turning over in bed, looking up, getting up, or lying down in bed. It is believed to be caused by calcium debris within the posterior semicircular canal (canalithiasis). The semicircular canals detect angular head accelerations. Debris in the canal causes inappropriate movement of the endolymph causing the erroneous sensation of spinning when the head shifts with respect to gravity. Most causes of BPPV are idiopathic or related to minor head injury; however, many different precipitants have been proposed. Patients tend to experience recurrent episodes of vertigo that last 1 min or less. Associated symptoms include nausea and vomiting. Hearing loss is usually absent and patients have no other neurologic complaints. Episodes may recur for weeks without therapy. Provoking symptoms and nystagmus with maneuvers such as the Dix-Hallpike maneuver support the diagnosis. With this maneuver, nystagmus and vertigo usually last less than 30 s; after it stops and the patient sits up, the nystagmus will recur but in the opposite direction. Repeating the maneuver on the same side will diminish the intensity of the nystagmus. Further testing is not indicated in typical BPPV, and neuroimaging is reserved for patients with symptoms that are not typical or those who present with other red flags [7].

Meniere's Disease

Meniere's disease is believed to be caused by abnormal fluid balance in the inner ear and associated with episodic vertigo (rotational nystagmus with episodes lasting up to 24 h), tinnitus (low pitch), and sensorineural hearing loss. It is unclear why fluid builds up in the endolymphatic spaces of the inner ear. The diagnosis is made based on clinical features as no specific testing is confirmatory. Audiometry should be performed in all patients with suspected disease. Brain MRI is

often indicated to rule out CNS tumors (acoustic neuroma) and vascular malformations. Patients should be referred to ENT early in the disease process as even though vertigo attacks may be controlled in most patients, hearing loss can be progressive.

Labyrinthitis/Vestibular Neuritis

Vestibular neuritis is believed to be an acute viral or postviral inflammatory process involving the vestibular portion of the eighth cranial nerve. It should be noted that the majority of patients do not necessarily report symptoms of a preceding viral illness [1]. It typically presents as an acute vertigo with nausea, vomiting, and gait impairment. In isolated vestibular neuritis, auditory function is preserved, whereas if the patient has unilateral hearing loss, the condition is defined as labyrinthitis. Patients with unilateral sensorineural hearing loss should be referred for audiometry. If no identifiable cause is found for this defect, imaging of the posterior fossa and internal auditory canal should be considered. There are no confirmatory tests for vestibular neuritis or labyrinthitis, and the diagnosis is made on a clinical basis. Patients with inconsistent exam findings, older patients, and those with new headache or any focal neurologic signs should undergo CNS imaging to rule out acute central vascular events of the brainstem and cerebellum [5].

Migrainous Vertigo

Migrainous vertigo affects about 3% of the population and 10% of migraineurs. Although this is a diagnosis of exclusion, it should be considered in patients who have a history of migraine or present with headache with associated migrainous features and associated symptoms (aura, photophobia, phonophobia, etc.). As with any vertiginous patient, those with red flag symptoms should be referred for imaging to exclude a central cause.

Presyncope

Presyncope is the prodromal symptom of impending loss of consciousness and is more common than actual syncope. The evaluation of these patients is very similar to patients who experience true syncope. As with dizziness, an open-ended history is essential to pursuing the appropriate diagnostic steps. Orthostasis is the most common cause of presyncope. It usually occurs when a patient is in an upright or seated position or when transitioning from a supine to standing position. Orthostasis can be caused by intravascular volume depletion, medications, and autonomic dysfunction [1]. Patients with vasovagal or neurocardiogenic presyncope may report a prodrome described as feelings of warmth, lightheadedness, diaphoresis, nausea, and visual darkening. Witnesses of the event may also describe pallor. Such episodes may be precipitated by specific situations (coughing, sneezing, micturition, stressful events, etc.). Syncope that occurs while supine, with exertion, or suddenly (without prodrome) should raise clinical suspicion for malignant cardiac arrhythmias (ventricular tachycardia, high-grade heart block, prolonged sinus pauses) or structural cardiac abnormalities (severe aortic stenosis or hypertrophic obstructive cardiomyopathy). All patients should be assessed for cardiac history or risk factors and should undergo orthostatic vital sign measurement and a careful review of their medication list. In addition, ECG testing should be done to detect anomalies such as prolonged QT interval, heart block/conduction disturbance, and tachy–/bradyarrhythmias [8]. Indwelling cardiac devices should be checked to ensure proper function. Additional testing including ambulatory cardiac monitoring, event monitoring, and/or echocardiography will depend upon the clinical scenario.

Disequilibrium

Disequilibrium is a sense of imbalance that occurs with walking or standing. It represents a disturbance in balance or coordination which leads to ambulatory impairment.

Determining the cause of dizziness in older patients can be challenging because it is often multifactorial, as patients often have several comorbid disorders and are on many medications which serve as possible contributors. The most common cause of disequilibrium in this population is multiple sensory deficit syndrome wherein multiple issues impair the patient's ability to ambulate unassisted [9]. Visual impairment, deafness, peripheral neuropathy, muscle weakness, and deconditioning can all contribute to dysfunction. This patient's gait is usually hesitant and apprehensive. Metabolic disease such as hypothyroidism, hypoglycemia, anemia, and adrenal insufficiency may be associated with disequilibrium. Movement disorders such as early Parkinson's disease may manifest with disequilibrium prior to the development of tremor and other characteristic features [9].

Lightheadedness

Psychiatric disorders (anxiety, depression, somatization disorder, personality disorder) and fibromyalgia are often the primary cause of nonspecific dizziness. Nonspecific dizziness may also be caused by hyperventilation. Purposeful hyperventilation, where the patient is positioned in a supine position and asked to breathe deeply and rapidly (30-times per minute) through their mouth, can be diagnostic if the technique recreates the patient's symptoms [1]. Using this technique can be reassuring and this revelation may provide therapeutic value.

Key History and Physical Exam

The most important step in determining the cause of the patient's dizziness is to set an environment conducive for the delivery of an unbiased description of what the patient is actually experiencing. As the clinician patiently listens, they are receiving clues that will help them categorize the patient's symptoms into one of the four major categories of dizziness.

In addition, as with any symptom evaluation, the duration, characteristics, precipitating/alleviating factors, and associated symptoms or features such as hearing loss should be discussed. The history should also include a review of the patient's medications as well as a dietary review for substances containing caffeine (which may lead to tachyarrythmias) or alcohol (which through direct toxicity or abrupt discontinuance can precipitate symptoms).

Duration of symptoms can assist with narrowing down the cause of vertigo. For example, BPPV and Meniere's disease tend to cause episodic vertigo, whereas persistent symptoms are more likely caused by vestibular neuritis or labyrinthitis. It should be noted that even when a vestibular lesion is permanent, vertigo subsides over days to weeks as the CNS adapts to the defect. As a result, vertigo is never a permanent or continuous symptom [10]. Some patients reporting long duration of symptoms are often described as having a continuous predisposition to vertigo or are describing a nonvestibular type of dizziness. In addition, patients should be asked about and evaluated for hearing impairment as hearing loss and tinnitus are suggestive of peripheral lesions and can be seen in labyrinthitis and Meniere's disease. These symptoms are not seen in vestibular neuritis or BPPV [1].

The goal of the physical exam is to reproduce the patient's symptoms and make note of any abnormal findings. The special additional maneuvers/tests should be decided upon based on the working differential diagnosis derived from the patient's history. In general, all patients should undergo an assessment for positional changes in blood pressure to detect orthostatic hypotension as well as an otologic (to evaluate for OME [otitis media with effusion]/AOM [acute otitis media]), cardiac, and neurological evaluation [10].

Dix-Hallpike Maneuver

The Dix-Hallpike maneuver should be performed in all patients with suspected vertigo as this test is 50–88% specific for BPPV [11]. These maneuvers are performed with the goal

of reproducing vertigo and nystagmus and are more useful in patients who do not already have symptoms and nystagmus at rest. This maneuver is initiated with the patient in a seated position. The examiner rotates the patient's head 45° to one side and then rapidly places the patient in a supine position while allowing the head to hang about 20° over the end of the table. The examiner should focus on the patient's eyes for about 30 s to evaluate for nystagmus. If no nystagmus is appreciated, the patient is returned to an upright position and observed for 30 s for nystagmus, and then the maneuver is repeated with the head turned to the opposite side. There is usually a latency of a few seconds before the patient develops nystagmus and symptoms. In such cases the nystagmus usually lasts less than 30 s. After the patient sits up, the nystagmus may recur in the opposite direction. If nystagmus is precipitated with this maneuver, it should be repeated on the same side. In BPPV the intensity and duration of the nystagmus should diminish with each repetition [11]. It should also be noted that the affected ear is the one that is down facing on provocation of nystagmus with this maneuver.

Nystagmus

The presence of nystagmus suggests that the dizziness is vertigo. Nystagmus is a rhythmic oscillation of the eyes. One function of the vestibular system is to maintain gaze during head movement through the vestibular ocular reflexes. A unilateral lesion leads to pathologic asymmetry in the vestibular system. This results in a slow drift of the eyes away from the target followed by a fast corrective movement in the reverse direction. The eyes will beat in the direction of the fast phase. This spontaneous nystagmus will continue until normal vestibular function is restored or until the CNS adapts to the lesion [6]. In a peripheral lesion, the fast phase is away from the affected side, and nystagmus increases in frequency and amplitude with gaze toward the side of the fast phase. When there is suspicion of a central cause, a detailed exam should be performed to search for cranial nerve abnor-

malities, motor or sensory changes, dysmetria, or abnormal reflexes. However, the absence of other neurologic signs does not exclude a central process.

Hearing Evaluation

There are several options for evaluation of hearing in the office setting. A rough evaluation for asymmetric hearing impairment can be performed by having the patient repeat words that are softly whispered into each ear or by having the patient close his or her eyes and identify the ear near which the examiner is rubbing fingers together. The Weber and Rinne test can distinguish between conductive hearing loss (CHL) and sensorineural hearing loss (SNHL). In the Weber test, a vibrating tuning fork is placed in the midline of the forehead. In normal hearing, the sound should be heard equally in both ears; however, in conductive hearing loss, the sound lateralizes to the affected ear, and in sensorineural hearing loss, the sound lateralizes to the unaffected ear. The Rinne test compares air conduction of sound vs. bone conduction of sound. In this test, the vibrating tuning fork is placed and held on the patient's mastoid process; when the sound can no longer be heard in that position, the tuning fork is then moved directly in front of the ipsilateral ear. In a normal exam the patient should be able to hear the tuning fork again, demonstrating that air conduction is greater than bone conduction. In a positive test the patient cannot hear the tuning fork again when it moved from the mastoid process to directly in front of the ear. This result demonstrates that bone conduction is greater than air conduction, suggesting conductive hearing loss. For example, on evaluation with the Weber test, if the sound is heard equally in both ears, the exam is normal. However, if the sound is heard louder in the right ear, this could indicate either CHL in the right ear or SNHL in the left ear. In the same patient, the Rinne test is then performed on the right ear; if bone conduction is greater than air

conduction, then CHL is confirmed in the right ear; however, if the Rinne test is normal on the right ear (air conduction > bone conduction), SNHL of the left ear is suspected.

Head Impulse Test, Skew Deviation, Saccadic Pursuit, and Direction-Changing Nystagmus

The head impulse test demonstrates integrity of the vestibulo-ocular reflex. The examiner sits in front of the patient and places hands on each side of the patient's head. The patient should focus on the clinician's nose and the clinician focuses on the patient's eyes. If the reflex is intact, the patient's eyes can remain focused on the clinician's nose during rapid head movements to both sides. If there is impairment in the peripheral vestibular system, the vestibulo-ocular reflex will be abnormal causing the eyes to move away with head movement toward the affected side which is followed by the patient's eyes quickly moving back to the clinician's nose (corrective saccade). In patients with acute vertigo, a normal vestibulo-ocular reflex bilaterally is suggestive that the cause of dizziness is central. Skew deviation is demonstrated when one eye is vertically aligned higher than the other, a sign of cerebellar or brainstem disease. Abnormal visual tracking is detected by asking the patient to follow a slowly moving target such as the clinician's finger both horizontally and vertically, while keeping the head still. The pursuit should be smooth. However, with cerebellar or brainstem disease, quick catch-up movements are noted and are called saccadic pursuit [10, 12].

Many patients with acute vertigo will have spontaneous nystagmus when looking straight ahead. In both central and peripheral vertigo, the nystagmus will worsen when a patient looks in the direction of the quick component (fast/corrective phase). In peripheral disease when the patient looks in the opposite direction (slow component), the nystagmus will disappear or diminish. However, in some patients with stroke,

when looking to the opposite side, the nystagmus can reverse denoting a direction-changing nystagmus. In peripheral disease nystagmus diminishes during fixation on an object; in central disease the nystagmus is unchanged [6].

Romberg Testing

Romberg testing can stimulate disequilibrium. The patient stands upright, feet together, with arms at sides and then asked to close his or her eyes. Symptoms of tilting or falling with eyes closed may suggest disordered proprioceptive and vestibular function. Symptoms with eyes open or closed may suggest cerebellar disease [12].

Other Diagnostic Testing

Other studies such as laboratory tests (CBC, serum chemistry, thyroid function tests) and radiography are not often beneficial and have low diagnostic yield without other supporting findings. MRI of the brain is indicated in patients with findings suggestive of central vertigo or acoustic neuroma. CT scans are less sensitive for detecting brainstem pathology but can be performed with thin cuts through the brainstem/posterior fossa. MRA sensitivity and specificity exceed 95% in detecting stenosis or occlusion of the posterior circulation [10, 12].

Treatment

Successful treatment of dizziness is predicated on a meticulous evaluation to determine the disease process responsible for the patient's symptoms. Most treatment strategies are based on relieving the underlying cause of the symptoms (see Table 25.2).

Table 25.2 Treatment pearls for the dizzy patient

Type of dizziness	Management
Migrainous vertigo	NSAIDS
	Triptans
	Evaluate need for prophylaxis
Disequilibrium	Reduce polypharmacy
	PT/OT referral
	Vision/hearing screening
	Ambulatory assist device
Meniere's disease	Audiometry
	Diuretics
	Referral to ENT
Labyrinthitis	Audiometry
	Steroids × 10 days
	Supportive therapy
BPPV	Epley maneuver
	Antihistamines if frequent attacks
	Vestibular rehab
Vestibular neuritis	Steroids × 10 days
	Supportive therapy
	Vestibular rehab
Lightheadedness	Treat underlying disorder
	Controlled breathing
	Behavioral health referral

BPPV

The majority of patients with BPPV achieve remission with particle repositioning maneuvers such as the Epley maneuver, where the goal is to clear debris from the semicircular canal. It should be noted that these maneuvers may be effective when the history is highly suggestive of BPPV even when no nystagmus is appreciated. Some studies suggest that a single maneuver is effective in 85% of patients. The Epley maneuver is performed by having the patient sit upright on the exam table with head rotated to the right (affected ear); the patient is then laid in a supine position with the head hanging over the end of the table. The patient's head is then rotated to the left, and the patient's head and body are rotated an additional 90° until the patient's nose is angled toward the ground. This position is held for 30 s and the patient is briskly returned to a seated position. This technique is repeated until no nystagmus can be detected. Videos of this sequence can be seen on NEJM clinical videos or on youtube.com. Modified versions of the Epley maneuver can be taught to patients for self-treatment at home. Even after an effective maneuver is performed, patients may have milder symptoms for several hours to days. Medications are not useful for the brief episodes of vertigo associated with BPPV; however, when there is a high frequency of episodes, antihistamines and antiemetics can provide relief. Patients may also benefit from a referral for vestibular rehabilitation [13].

Vestibular Neuritis/Labyrinthitis

To relieve the suspected postviral inflammatory process involved in vestibular neuritis and labyrinthitis, patients should be prescribed a 10–14-day steroid taper. Antiviral agents have not been demonstrated to hasten recovery and are therefore not recommended. Patients should also be provided with other supportive care which may include volume replacement for severe nausea and emesis, antiemetics, and in some cases a referral for vestibular rehabilitation [1].

Meniere's Disease

The abnormal fluid balance of this condition can be managed based on the severity of disease. All patients should be referred for an ENT evaluation. Noninvasive treatments include salt restriction, diuretics, antihistamines, vestibular suppressants, and antiemetics. Patients should also be referred for vestibular rehabilitation. Patients with refractory or severe disease despite medical therapy may be candidates for invasive therapies such as intratympanic gentamicin or glucocorticoids and, in some cases, surgical therapy [1].

Disequilibrium

The evaluation of a patient with disequilibrium involves looking for other disorders that are contributing to the symptoms as treatment is focused on addressing the issues that underlie this condition. This may involve withdrawal of precipitating medications, referral for ophthalmologic evaluation and corrective lenses for visual impairment, providing an ambulatory assistive device (cane or rolling walker), physical therapy evaluation, and the treatment of any metabolic, neurologic, or movement disorders that were unveiled during the evaluation.

Presyncope

The evaluation of patients with presyncope is the same as for patients who experienced true syncope. As with all other causes of dizziness, the history guides the clinician to the appropriate exam and relevant testing needed to secure the diagnosis. Any potentially offending medications that can safely be tapered or discontinued should be a priority. Patients with orthostatic hypotension can benefit from volume replacement if they are volume depleted. Refractory orthostasis should prompt the clinician to consider autonomic dysregulation. In addition to management of underly-

ing metabolic and endocrine disorders, medications such as midodrine or fludrocortisone can be initiated. Patient education with behavior modification should be provided to patients with a neurocardiogenic process. Patients with atherosclerotic cardiovascular disease history or risk factors, those with sudden or exertional syncope, and those who experience syncope in a supine position should undergo thorough evaluation and treatment for potentially malignant causes [13].

Lightheadedness

Hyperventilation syndrome often coupled with psychiatric disorders (anxiety and depression) is the main contributor to the vague and imprecise symptoms of lightheadedness. As previously noted, if the hyperventilation provocation test successfully recreates the patient's symptoms, this can also be therapeutic and reassuring to the patient [1]. Conscious breathing exercises can control future events. If a mood disorder is revealed during symptom evaluation, this should be treated with the appropriate agents, and the patient can also be referred to the relevant behavioral health specialist.

Clinical Pearls

- The patient's initial, raw, unguided description of symptoms is the most important step in determining the cause of dizziness.
- Movement worsens all types of vertigo, and even though patients with peripheral vertigo may not want to move, they are usually able to walk. In comparison, patients with central vertigo experience greater impairment in gait and posture and are often very ataxic and unable to walk.
- All patients with Meniere's disease should be referred to ENT early in the disease process as even though vertigo attacks may be controlled in most patients, hearing loss can be progressive.

- Orthostasis can be caused by intravascular volume depletion, many medications, and autonomic dysfunction.
- Visual impairment, deafness, peripheral neuropathy, muscle weakness, and deconditioning can all contribute to disequilibrium.
- The hyperventilation test for suspected lightheadedness can be both therapeutic and diagnostic.

Do Not Miss This!

- These are findings on the physical exam that suggest stroke in dizzy patients: normal bilateral vestibulo-ocular reflexes (noted on head impulse test), skew deviation, abnormal visual tracking (saccadic pursuit), and direction-changing nystagmus.
- Syncope that occurs while supine, with exertion, or suddenly (without prodrome) should raise clinical suspicion for malignant cardiac arrhythmias (VT, high-grade heart block, prolonged sinus pauses) or structural cardiac abnormalities (severe aortic stenosis or HOCM).

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Chapter 26
Headache

Schantal Polanco

Abbreviations

AVM	Arteriovenous malformation
CDH	Chronic daily headache
CVT	Chronic venous thrombosis
GCA	Giant cell arteritis or temporal arteritis
HC	Hemicrania continua
LP	Lumbar puncture
MO	Medication overuse
PH	Paroxysmal hemicranias
SAH	Subarachnoid hemorrhage
SDH	Subdural hematoma
SUNCT	Short-lasting unilateral neuralgiform headache
TAC	Trigeminal autonomic cephalalgia
TMJ	Temporal mandibular joint
TTH	Tension-type headache;

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Introduction

Headache is a common neurological complaint in the outpatient setting [1]. The importance of proper diagnosis is crucial to our management. Most headaches are of benign etiology and fall under the category of primary headache disorders. Tension-type headache is more common than migraine headache [2]. However, migraine headaches tend to be disabling and cause functional impairment leading patients to seek medical assistance more frequently for this ailment [2]. Cluster headaches fall under the category of trigeminal autonomic cephalalgia and this disorder has a prevalence of less than 1% [3]. It is important to recognize the characteristics and diagnostic criteria of primary headaches to assist with management. As an initial first step in our assessment, it is important to focus on key aspects of the history and physical examination to exclude secondary causes of headache which may stem from other systemic, neurological, psychiatric, or traumatic etiologies. Once these "red flags" in the history and physical examination are excluded, one can focus on the more common primary etiologies of headache (Fig. 26.1).

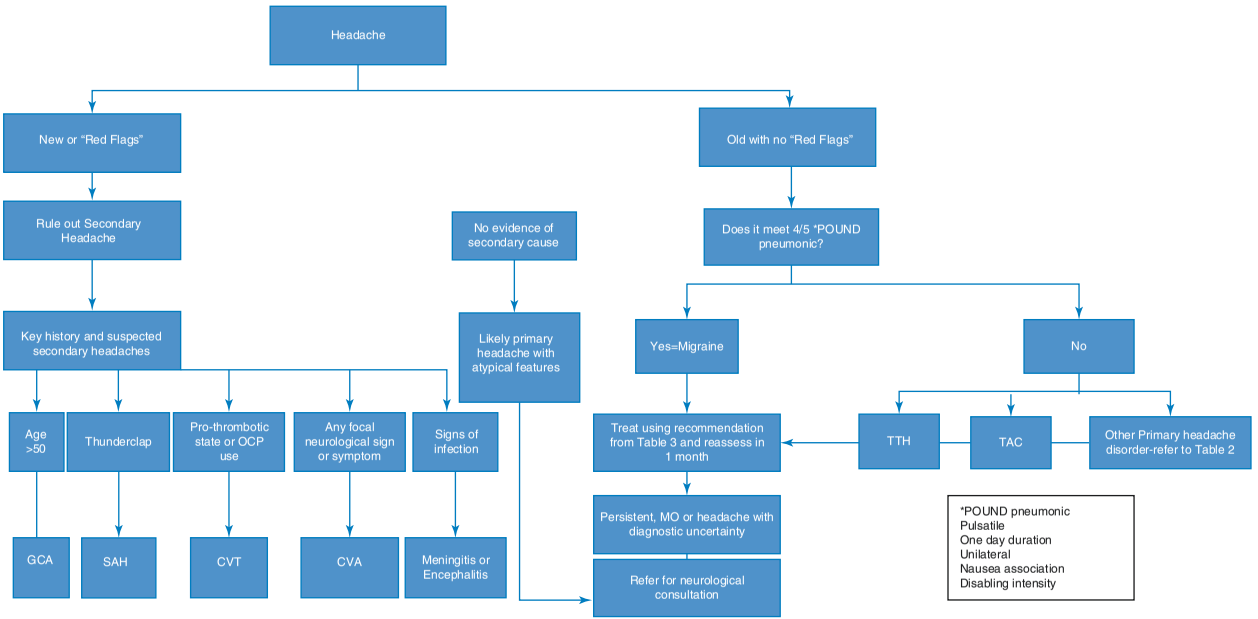

FIGURE 26.1 Headache algorithm

Key History and Physical Exam

A complete history and physical examination are essential in the assessment of any headache. When done properly, the potentially dangerous causes of headache which may warrant emergent intervention can be identified. The following features in the history have been underlined to highlight information which may support a secondary cause of headache (refer to Table 26.1).

History

Age: New headache in a patient above 50 years should raise concerns for temporal arteritis, acute angle-closure glaucoma, and malignancy in the right context [1, 4–6], particularly if associated with visual disturbance, jaw claudication, polymyalgia, cough, or weight loss.

Onset and Characteristic: An abrupt onset of maximum intensity is suggestive of an ominous or secondary cause for the headache. These symptoms fall under the umbrella term of "thunderclap headache" typically described by patients as "the worst headache of my life" and warrants immediate attention with imaging and lumbar puncture when imaging is nonrevealing and our clinical suspicion is high. Etiologies

Table 26.1 Differential diagnosis as outlined by the International Headache Society

Primary headache	Secondary headache based on "red flags"
1. Tension-type headache (TTH) 2. Migraine 3. Trigeminal autonomic cephalalgias (TACs)	Look for clues in your history, physical exam, laboratory studies, and imaging to guide your differential diagnosis when a secondary headache is suspected.

Table 26.1 (continued)

Primary headache	Secondary headache based on "red flags"
4. Other primary headache disorders • Primary cough headache • Primary exercise headache • Primary headache associated with sexual activity • Primary thunderclap headache • Cold stimulus headache • External pressure headache • Primary stabbing headaches • Nummular headache—Coin shaped • Hypnic headache—Only during sleep • New daily persistent headache	1. Headache attributed to infection. 2. Headache attributed to trauma. 3. Headache attributed to a vascular disorder (CVA, SAH, SDH, arteritis, unruptured vascular malformation, carotid or vertebral artery disorder, genetic vasculopathy, pituitary apoplexy, and other acute intracranial disorders such as those resulting from an endovascular procedure or conditions less clearly understood such as reversible cerebral vasoconstriction syndrome. 4. Headache attributed to other nonvascular intracranial disorder (cerebrospinal fluid pressure—High or low), noninfectious intracranial inflammatory diseases, intracranial neoplasm, seizure, Chiari malformation) 5. Headache attributed to substance exposure, use, or withdrawal (including those prescribed, illicit, and contained in food). 6. Headache attributed to a disorder of homeostasis (hypoxia, hypercapnia, dialysis, hypertension, hypothyroidism, fasting, etc.) 7. Headache attributed to disorder of facial or cervical structures. 8. Headache attributed to psychiatric disorder.

which may present this way include subarachnoid hemorrhage, cavernous venous thrombosis, pituitary apoplexy, hypertensive emergency, arterial dissections, and acute angle-closure glaucoma, which require emergent intervention [1, 4, 5].

Duration and Relevant *Past Medical History*: Persistent or progressive headache in a patient with a past medical history of cancer, HIV, Lyme disease, systemic vascular disorder, or hypercoagulable state warrants further workup of secondary causes. Additionally, patients with a past medical history of a primary headache such as migraine may be at increased risk of developing brain lesions including posterior circulation stroke-like lesions [7]. A new headache or prior changes in the characteristics of a known headache disorder warrant further investigation.

Medications: Use of anticoagulants, NSAIDs, steroids, or drugs of abuse such as cocaine place patients at an increased risk of intracranial bleed and can be an indication for neuroimaging [1]. The use of birth control pills is associated with increase in migraine severity but also an increased risk of CVT [8, 9].

Context: Headache in the setting of trauma, uncontrolled hypertension, motor, sensory, cerebellar, personality, or cognitive change warrants imaging to further investigate the neurological symptom. The presence of systemic symptoms should precipitate additional considerations. In patients who were hospitalized with COVID-19, headache was considered a presenting symptom and this diagnosis should be considered in the appropriate clinical context [10].

Aggravating factors that raise intracranial pressure such as exertion, cough, and lying down may reflect an intracranial etiology and require additional investigation [4].

Location: Careful history and palpation over maxillary and frontal sinuses, orbits, temporal artery, TMJ, ears, occipital nerve, and upper posterior neck can reveal pain from various secondary headaches and neuralgias [5].

Physical Examination

Relevant Vital Signs: Hypertension and obesity can point towards a secondary diagnosis of hypertensive encephalopathy, pseudotumor cerebri (idiopathic intracranial hypertension), or more benign causes of secondary headaches such as sleep apnea in the appropriate context. Fever, rash, and/or meningismus must be worked up immediately for infectious etiology and an LP must be performed.

Palpation: Palpation over maxillary and frontal sinuses, the orbits, the temporal artery, and TMJ as well as the ear, occipital nerve, and upper posterior neck can reveal pain stemming from myofascial or joint dysfunction among other secondary headaches and neuralgias [5].

Funduscopic and Full Neurological Examination: Papilledema and any focal neurological sign or symptom other than typical visual or sensory aura ("typical" only if patient has a history of a similar pattern lasting 60 min or less) necessitate further investigation, such as neuroimaging, to rule out mass lesion and serologic testing to rule out collagen vascular disease [4, 5].

Once the red flags in the history and physical exam have been excluded, the diagnosis of primary headache syndrome should be investigated. Various tools are available to aid in the diagnosis of primary headache disorders. Some of these tools include headache questionnaires and diaries to aid in determining the frequency and disability caused by the primary headache [11, 12]. To begin classifying primary headaches, identifying a potential migraine headache is a reasonable start. Migraine headache is a frequent cause of severe headache that is often not diagnosed and treated properly leading to significant disability [13]. The five criteria most predictive of migraine can be remembered by the POUND mnemonic (pulsatile quality, one-day duration, unilateral, nausea or vomiting with disabling intensity) [14, 15]. Patients meeting 4/5 of the POUND criteria have a greater than 90% chance of a having a migraine headache [14, 15].

Further evaluation and diagnosis of primary headache etiologies are outlined by the International Headache Society (refer to Table 26.2). Once an accurate history is obtained, primary headaches can be classified based on four main categories to aid with management.

Table 26.2 Diagnostic criteria of primary headache disorders as outlined by the International Headache Society

1. Tension-type headache (TTH) diagnostic criteria.

At least two of the following four characteristics:
- Bilateral location
- Pressing or tightening (nonpulsating) quality
- Mild or moderate intensity
- Not aggravated by routine physical activities such as walking or climbing stairs

Both of the following:
- No nausea or vomiting
- No more than one of phonophobia or photophobia

Lasting 30 min to 7 days and not better accounted for by another international classification of headache disorders, third edition (ICDH-3) diagnosis

2. Migraine headache diagnostic criteria

The diagnostic criteria for migraine headache from the international headache society is as follows:

A. at least five attacks fulfilling criteria B to D
B. Headache attack lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
   - Unilateral location
   - Pulsating quality
   - Moderate or severe pain intensity
   - Aggravation by or causing avoidance of routine physical activity
D. during headache at least one of the following:
   - Nausea and/or vomiting
   - Phonophobia and photophobia

Not better accounted for by another ICDH-3 diagnosis

Table 26.2 (continued)

3. Trigeminal autonomic cephalalgias (TACs) which include cluster headache

Five attacks of severe, unilateral pain lasting 15–180 min with either of the following autonomic features ipsilateral to the headache:

- Lacrimation or conjunctival injection
- Rhinorrhea or nasal congestion
- Eyelid, forehead, or facial swelling
- Miosis
- Ptosis
- Ear fullness

Or

A sense of restlessness or agitation

Attacks occur in "clusters" lasting for weeks or months following a period of remission lasting months to years. Chronic is defined by a remission of less than 1 month.

4. Other primary headache disorders
   - Primary cough headache
   - Primary exercise headache
   - Primary headache associated with sexual activity
   - Primary thunderclap headache
   - Cold stimulus headache
   - External pressure headache
   - Primary stabbing headaches
   - Nummular headache—Coin shaped
   - Hypnic headache—Only during sleep
   - New daily persistent headache

Tension-type headache (TTH) is the most common primary headache disorder [16, 17]. TTH is usually mild in severity and relieved with over-the-counter medication. A large number of patients suffering from TTH have pericranial muscle tenderness making the palpation of pericranial muscles in the physical exam essential. Additional TTH subtypes are further described based on the frequency of episodes per month.

Migraine headache is the second most common type of primary headache disorder but tend to be the most disabling, leading patients to seek medical attention most frequently for this condition [16]. Subtypes of migraine are categorized as migraine without aura and migraine with aura. An aura is a transient neurological symptom during or preceding headache but can occasionally occur without headache. An aura may include visual, sensory, language, motor, brainstem, or retinal manifestations [12]. Most neurological symptoms last 1 h but motor disturbances may last up to 72 h [12]. Any headache with an acute neurological manifestation warrants intracranial imaging oftentimes making the diagnosis of migraine with aura a diagnosis of exclusion. Chronic migraine is differentiated from episodic migraine if the attack occurs >15 days per month for more than 3 months with features of migraine at least 8 days per month [12]. Chronic migraine warrants preventive treatment and a neurological consultation.

The least common type of primary headache disorders fall under the category of trigeminal autonomic cephalalgia of which cluster headache is the most common. Other trigeminal autonomic cephalalgias have similar symptoms but diagnostic criteria differ based on frequency and duration of symptoms [18]. Cluster headaches last 15–180 min, and paroxysmal hemicrania (also described as indomethacin-responsive headache) occurs several times a day and last 2–30 min, while hemicrania continua is present for greater than 3 months. Other short-lasting neuralgiform headache attacks such as SUNCT also fall under this category [18].

Once a primary headache disorder is diagnosed, treatment options can be explored (refer to Table 26.3). Once adequate treatment is initiated, it is important to reassess response and the frequency of both recurrent headache and medication use. Primary headache disorders that are frequent and chronic leading to the use of medication >10 days per month for more than 3 months can result in medication overuse headache [19, 20] which warrants a different treatment approach and a neurology consultation. In patients with con-

Table 26.3 Treatment of common primary headache disorders

Type	TTH	Migraine	Cluster	CDH attributed to MO
Treatment options	Aspirin, acetaminophen, NSAIDs, or combination of aspirin, Tylenol, and caffeine typically enough to provide relief. Frequent TTH respond best to abovementioned therapy in addition to therapy aimed at reducing stress, anxiety, and depression [23]. Muscle relaxation to reduce stress and muscular pain is also recommended [20].	Mild: NSAIDs ± metoclopramide. Refractory or severe: Triptan Ergotamine Frequent attacks (>5 days per month) need preventive treatment with beta blockers, amitriptyline, venlafaxine, and/or antiepileptic such as valproic acid and topiramate [20, 23]. Additional preventive therapies with onabotulinumtoxinA and monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or the CGRP receptor may be considered by neurology specialists [22]. Additional acute and preventive therapies including lasmiditan, a selective 5-HT receptor agonist, as well as monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or the CGRP receptor may be considered by the neurology specialist [24]. In selective cases noninvasive neuromodulation therapies (transcranial nerve stimulation, vagal nerve stimulation, and supraorbital nerve stimulation) may be considered by the specialist for the treatment and prevention of migraine headaches [25]	Oxygen Triptan Ergotamine—Before anticipated attack Persistent or frequent need preventive treatment with short course of steroids plus verapamil, valproate, and/or lithium in refractory cases [20, 23]	Withdraw overused medication and allow headache to revert to episodic pattern [17]. Behavioral therapy and acute treatment of primary headache disorder are recommended [19].

Adapted from references [15, 17, 19, 20, 22–25]

traindications to pharmacological options, a neurology consultation for consideration of nonpharmacological treatment with transcranial magnetic stimulation or vagal nerve stimulation can be considered [21, 22].

Melatonin and supplements including magnesium may be helpful in the prevention of migraine headaches but larger clinical trials are needed to determine the effects of such treatment [26, 27].

Discussion of migraine treatment and prevention should also include trigger avoidance and behavioral modification. Relaxation via biofeedback training and cognitive behavioral therapy has decreased the frequency of attacks in many and has helped promote lifestyle changes necessary for optimal health and symptom control [28]. These alternative and complementary therapies should be offered to patients when available.

Clinical Pearls

- The initial assessment of headache requires a through history and complete physical examination to exclude secondary causes of headache which may be life-threatening.
- Once these red flags are identified, it is important to proceed with neuroimaging and/or LP for proper diagnosis. In the absence of positive findings if clinical suspicion remains high, treatment may be warranted pending further investigation as in the case of temporal arteritis.
- Once secondary causes of headache are excluded, one can start considering more common benign primary headaches. To begin classifying primary headaches, identifying migraine headaches is a reasonable start.
- Patients meeting 4/5 of the POUND criteria have a greater than 90% chance of having migraine headaches and should be treated accordingly. Exclusion of POUND criteria should prompt further evaluation of other primary headache etiologies.
- All primary headaches can develop into chronic primary headaches if duration of headache fits this description. However, the most common type of chronic headache

remains medication overuse as a complication of persistent symptoms highlighting the need for reassessment once therapy is commenced.
- Persistent symptoms despite treatment warrants further workup to rule out secondary causes and a formal neurology consult.

Do Not Miss this!
Most headaches are of benign etiology but secondary etiologies can be life-threatening and must be ruled out. Trauma, age above 50 years, systemic signs, immunocompromised state, or any neurological symptom should prompt neuroimaging and additional investigations to rule out suspected etiology.

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Part VIII
Gynecologic

Chapter 27
Vaginal Discharge

Lucille M. Torres-Deas, Nicole C. Habibe Burgos, and Athina Vassilakis

Introduction

Vaginal discharge accounts for almost 10 million annual visits to primary care clinics in the United States [1–3]. Although most commonly physiological, it may be a symptom of an underlying infection or other abnormality. Here, we will review history, physical exam, and testing and will present a patient-centered approach for treatment, risk reduction, prevention, and education.

Physiological vaginal discharge is typically white or clear and changes in accordance with the menstrual cycle [4]. Abnormal discharge may be yellow, green, or curdy white color and may contain blood or have a foul odor. It may occur with associated symptoms or it can occur alone.

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Although there are many etiologies of abnormal discharge, the predominant etiologies (70% of all causes [2, 3]) are bacterial vaginosis, vaginal candidiasis, and vaginal trichomoniasis. Other infectious causes include cervicitis caused by sexually transmitted infections such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Noninfectious causes include atrophic vaginitis, contact or allergic dermatitis, or retained foreign body vaginitis. Structural etiologies of abnormal discharge may include cervical polyps, fistulas to the bladder or rectum, and other gynecological tumors.

History

A thorough history is key in diagnosing the etiology of vaginal discharge.

Knowing a patient's medical conditions is important to frame the baseline risk of diseases for each patient. Low estrogen level, diabetes, or other immunocompromised states and recent or current medication usage including antibiotics or hormones (steroids) are of particular interest [5].

The history should include the onset, duration, amount, color, and odor of the discharge. Associated history like redness or inflammation, itching, bleeding, fever, and pain can assist with determining differential diagnoses [6].

History should also include a patient's last menstrual period, typical length of cycle, and typical variation in discharge volume and consistency. This can help elucidate changes from a patient's baseline and pinpoint the menstrual cycle phase of the patient to correlate with the expected type of discharge. For example, during ovulation, the discharge may become thinner and clearer, while after ovulation it can become thicker and stickier. It is also critical to determine if a patient is pregnant, post-partum, or lactating or has recently had a miscarriage or abortion, as these could cause bleeding or discharge and/or impact treatment recommendations.

It is important to determine any exposure to fragrant soaps, body gel, feminine hygiene products, douches, or vaginal devices, which can result in irritation and/or change in vaginal flora, leading to infection.

Social history should be elucidated to determine if there are any risk behaviors and/or trauma that require additional screening, intervention, and/or risk reduction education. Traditional risk factors for sexually transmitted infections (STIs) can be reviewed [7]. Screening for sex trafficking and drug and alcohol use is necessary, as they may pose increased risk for STIs. In addition, obtaining prior history of incarceration, detainment, and financial instability will be essential in creating a patient-centered approach to screening, diagnosis, treatment, prevention, and education.

Traditional risk factors for STIs include: *

1. Age <25 years.
2. Symptoms of STIs in partner.
3. New sexual partner for the last 3 months.
4. Two or more sexual partners for the last 6 months.
5. No/sporadic usage of condoms.
6. History of previous STIs.

*These are traditional risk factors for STI testing which were included in studies, which may not be inclusive. We should take a patient-centered approach to ensure we are not perpetuating stigma and bias, i.e., age or prior experiences [7, 8].

If a patient meets one or multiple of these risk factors, STI screening is generally recommended.

Figure 27.1 outlines history factors that should trigger some level of examination. In the absence of these, diagnosis based on history alone can be appropriate [8, 9].

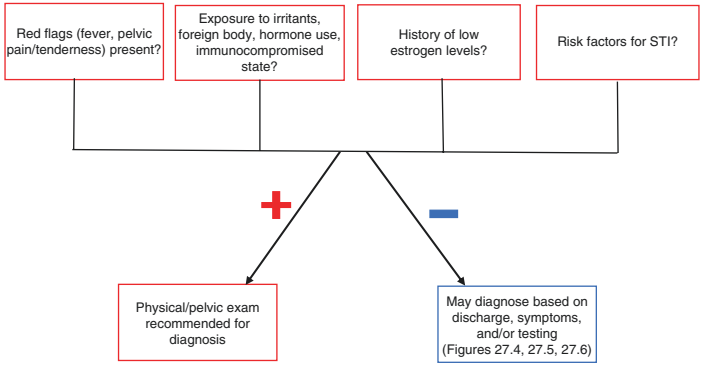

FIGURE 27.1 Initial assessment

Physical Exam

First, vital signs and a general exam assessment should be obtained. Concerning signs include visible distress, diaphoresis, and/or abnormal vital signs such as hypotension, tachycardia, and/or fever. An abdominal exam should also be performed to determine if the patient has abdominal and/or suprapubic pain. When doing a vaginal and/or pelvic exam (Fig. 27.1), obtain consent and introduce a trained chaperone before proceeding. Endocervical swabs may be collected at the time of examination. The literature supports that the majority of women find self-collected vaginal swabs easy to obtain and prefer this method over a pelvic exam or clinician-collected swab. [10]

External vaginal exams may reveal obvious discharge, erythema, or inflammation (vulvovaginal dermatitis) [6]. Vesicles may point to herpes simplex virus, which is discussed in Fig. 27.2.

Pelvic exam should be completed when a patient has any red flag symptoms, low estrogen level, immunocompromised states, exposure to irritants or foreign bodies or reports high-risk sexual behavior. Table 27.1 delineates differential diagnoses based on physical/pelvic exam findings.

Herpes Simplex Virus (HSV)[19]

HSV is a highly contagious virus present in more than 67% of the world population. HSV-1 most commonly causes orolabial herpes but may also cause genital/anal herpes. HSV-2 is sexually transmitted and causes genital/anal herpes, which is more likely to recur than HSV-1. Infection with this virus is lifelong and herpetic lesions may be a common primary care complaint.

History Pearls

- Primary infection may present with prodrome of flu-like symptoms (fever, malaise, lymphadenopathy)
- Patient may complain of painful ulcers in or around the mouth, commonly described as cold sores on the lips
- They may experience tingling, itching, or burning sensation on lips, mouth, genitals or around the anus before appearance of lesions and lesions may often recur
- HSV can be transmitted from a mother with genital HSV to her infant during delivery
- Immunocompromised patients may experience more severe symptoms/recurrence
- Genital herpes may not have symptoms, but could present as one or more genital or anal ulcers (primary infection may cause flu-like illness), dysuria or genital pain
- Symptoms of recurrent episodes are commonly less severe than first outbreak, with amount of outbreaks decreasing over time

Physical Exam Findings

- Grouped vesicles on erythematous base
- Vesicles with scalloped borders
- Pustules, erosions, and ulcerations, possibly crusting over on healing lesions
- Lymphadenopathy
- Genital herpes may cause swelling of vulva

Diagnosis

HSV is often diagnosed through HSV serology or viral PCR. As a sexually transmitted infection, genital herpes may warrant further STI workup to test for gonorrhea, chlamydia, HIV, and syphilis.

Treatment

- *First Episode:*
  - *Orolabial:* Valacyclovir 2g BID x 1 day
  - *Genital:* Acyclovir 200mg PO 5x daily x 5-10 days, acyclovir 400mg PO 3x daily x 5-10 days, Valacyclovir 500mg-1g PO BID x 5-10 days, famciclovir 250mg PO 3x daily x 5-10 days
- *Recurrent:*
  - *Episodic therapy:*
    - *Orolabial:* Valacyclovir 2g BID x 1 day
    - *Genital:* Acyclovir 200mg PO 5x daily x 5 days, acyclovir 400mg PO 3x daily x 3-5 days, Valacyclovir 500mg PO BID x 3-5 days,
  - *Suppressive therapy:*
    - *Orolabial:* Valacyclovir PO 500mg daily (if <10 outbreaks/year) or Valacyclovir 1g PO daily (if >10 outbreaks/year). Immunocompromised patients may use Acyclovir 400-800mg 2-3x daily or valacyclovir PO 500mg BID
    - *Genital:* Acyclovir 200mg PO 4x daily, acyclovir 400mg PO BID, Valacyclovir 500mg PO daily, Valacyclovir 1g PO daily, or Famciclovir 150mg PO BID

Pregnant: Same as above
Counsel patient on use of condoms
Abstinence from sexual contact when patient has visible lesions

FIGURE 27.2 Herpes simplex virus (HSV) [11]

Table 27.1 Differential diagnoses: based on physical/pelvic exam suggestive findings [5, 6, 8, 12, 13]

Bacterial vaginosis (BV)	Vulvovaginal candidiasis (VVC)	Trichomonas vaginalis (TV)	Gonorrhea/ chlamydia
• White/grey homogeneous discharge • Fishy odor • No vaginitis/ vulvitis	• Thick, white curd-like discharge, may present without discharge • Erythema, edema • Vulvitis/ vaginitis • Excoriations	• Green/ yellow frothy discharge • Fishy odor • Vulvitis/ vaginitis, vaginal pain on exam • Erythema • If cervix visualized, may see petechiae or "strawberry cervix"	• Pain with pelvic exams • Discharge that does not fit any of the above descriptions, may present without discharge • If cervix visualized, may be friable, inflamed, erythematous

Can You Omit a Speculum Exam?

Standard of care is to perform speculum exam when a patient presents with discharge.

Studies have shown, however, that specimens collected from speculum exams (endocervical swabs) are unlikely to detect more sexually transmitted infections than clinician- or self-collected high vaginal swabs [4, 14]. Sensitivities for trichomoniasis detection was 75% with collection by speculum and 77% with collection by swab. The sensitivities for bacterial vaginosis (BV) are similar; thus, speculum exam was unlikely to result in more positive results. For vulvovaginal candidiasis (VVC), the speculum method might be more sensitive. When available, high vaginal swabs, whether self-collected or clinician collected, are the preferred specimen for gonorrhea and chlamydia screening. Although first-catch urine samples from women are acceptable for screening for

sexually transmitted infections, they may detect up to 10% fewer infections than high vaginal swab samples [10].

Cervical friability and presence of mucus are not highly sensitive or predictive of cervicitis, so speculum exams by themselves are not useful for reliable diagnosis of gonorrhea, chlamydia, trichomoniasis, BV, and candidiasis [14, 15]. Moreover, victims of sexual violence may experience more pelvic exam-related anxiety, distress, trauma, and/or fear [16]. Thus, pelvic examination should only be performed if absolutely necessary.

When Is a Bimanual Exam (BME) Necessary?

Bimanual exams generally have low sensitivity, even more so, for pelvic adnexal masses and in the setting of obesity [17, 18]. In the absence of lower abdominal pain or dyspareunia, *pelvic inflammatory disease* can be ruled out (100% negative predictive value) [16, 18]. However, if a patient has these symptoms, BME may be necessary to assess for cervical motion, uterine, and/or adnexal tenderness [16].

If a speculum or bimanual exam is performed, a trained chaperone should be present.

Other exam findings may include retained foreign body, which normally presents with bloody or brown discharge [19], anterior or posterior fistula, visible mass, cervical polyp, or vaginal atrophy. These findings may indicate a need for referral to a specialist. If a retained foreign body is visible, the clinician may attempt removal. However, if a foreign body is not visible but suspected or removal is unsuccessful, referral to a gynecologist for vaginoscopy, vaginal irrigation, or foreign body removal is indicated.

Diagnosis

Presumed diagnosis and choice of treatment can be guided by symptoms [9, 13]. Diagnosis guided by description of the discharge can be found in Fig. 27.3.

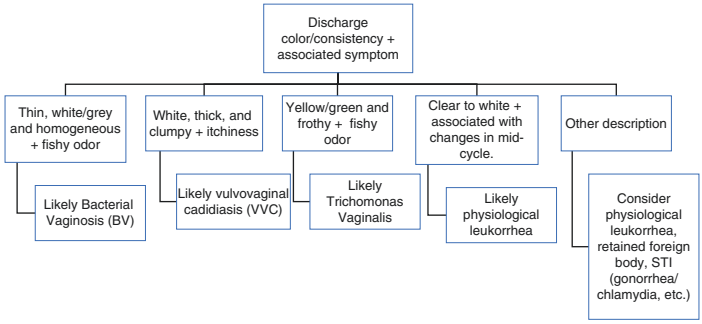

FIGURE 27.3 Flow diagram for differential diagnosis based on HPI [2, 5, 6, 8, 9, 12, 20]

Association and change of vaginal discharge with menstrual cycle points toward physiological leukorrhea, or normal vaginal discharge. Absence of fishy odor in the discharge likely rules out bacterial vaginosis, while presence of itching most likely points toward vulvovaginal candidiasis, and absence of itching rules it out [21].

Although diagnosis may be elicited based on HPI [9], vaginal discharge pH testing and microscopy often provide important supporting information [2, 15, 22]. When microscopy is not available, vaginal discharge should be collected using a loop or swab (either patient or clinician collected) and be tested using narrow range paper. Figure 27.4 reviews presumed diagnosis based on pH alone.

The Amsel criteria include the following (at least three of the following must be met) [5, 12, 15, 20]:

1. pH > 4.5,
2. Positive whiff test.
3. Thin white/grey and homogeneous discharge.
4. Presence of clue cells on microscopy.

When point-of-care microscopy is available, Fig. 27.5 details sample findings associated with each diagnosis. The clinician may use a sample from self-swab [10] or physical exam to examine discharge. The sample should be mounted on a microscopy slide and diluted in one or two drops of normal saline.

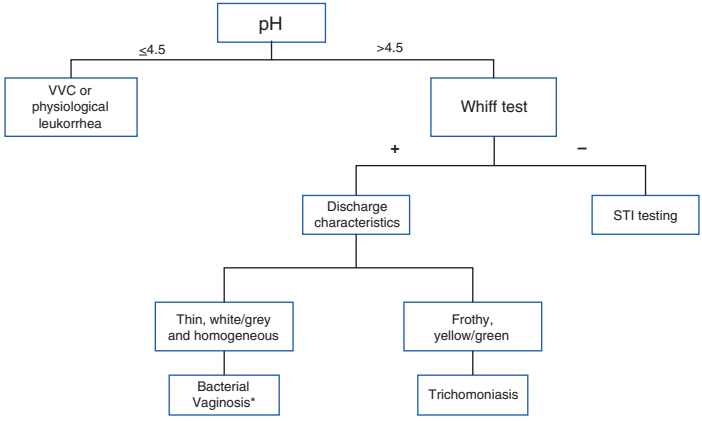

FIGURE 27.4 Initial testing if no microscopy available. (*Based on Amsel criteria) [2, 5, 8, 20]

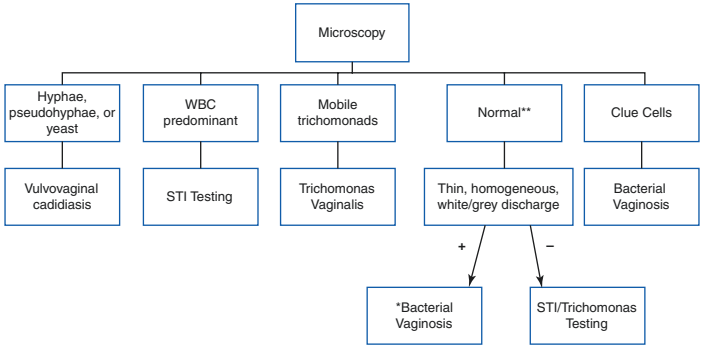

FIGURE 27.5 Diagnosis based on microscopy findings. (*Based on Amsel criteria) [2, 5, 23]

It is important to note that absent findings on microscopic examination does not necessarily rule out a diagnosis [2]. Additional testing may be done when results are inconclusive.

Contact or allergic vaginitis/vulvitis (Fig. 27.6) should be considered when a patient reports possible exposure to irritants or inserting devices into the vagina. These can also contribute to a change in vaginal pH/normal flora which increases the risk of bacterial vaginosis.

Vulvovaginal dermatitis[3]
Common etiologies of vulvovaginal dermatitis include atopic dermatitis, irritant contact dermatitis or allergic contact dermatitis. As pruritus is a very common symptom, clinicians should rule out vulvovaginal candidiasis.

History Pearls:

- History commonly includes pruritus and vulvar irritation;timeline is important to elucidate possible irritants or allergens that can cause dermatitis
- It is important to determine any exposure to fragrant soaps, body gel, feminine hygiene products, douches, or prescription products
- Abnormal discharge may be present
- Burning and itching are common in irritant/allergic dermatitis

Physical Exam Findings:

- *Atopic dermatitis:* poorly demarcated red itchy patches and thin plaques, excoriations, hypo-or hyperpigmentation due to repetitive trauma and scratching
- *Irritant/allergic dermatitis:* erythema, excoriations, edema, hypo-or hyperpigmentation

Treatment: **Patient education is super important**

- Topical anti-inflammatory agents: triamcinolone 0.1% ointment
- Control pruritus with antihistamines (hydroxyzine 10-25mg 3 to 4 times daily as needed)
- Eliminate irritants and allergens (topical hygiene products, deodorized pads/liners, lubricants, baths, salts,or oils) and carefully read product labels
- Repair barrier with petroleum jelly, dimethicone or zinc oxide paste 2-3x daily

FIGURE 27.6 Vulvovaginal dermatitis [3]

Additional Testing

Additional testing may be warranted due to uncertain results or recurrent infection. Culture of samples may detect candida and may be especially useful for recurrent candidal infections [12]. Nucleic acid amplification tests on urine or vaginal swabs can be used to identify chlamydia or gonorrhea. Although BV may be diagnosed clinically, there are additional BV tests that laboratories may perform and may be useful for recurrent infections [12]. There are also rapid antigen and nucleic acid amplification tests for trichomoniasis [2, 20].

Treatment

Table 27.2 outlines treatment options by diagnosis and highlights whether the patient's partner also needs to be treated. If a diagnosis of sexually transmitted infection is suspected, the patient should be treated empirically to prevent permanent complications of sexually transmitted infections.

Recurrent infections may prompt suspicion for reinfection from an infected sexual partner, an immunocompromising condition, or new sexual contacts.

If the patient is pregnant or lactating, you may consult the *InfantRiskCenter©* *https://www.infantrisk.com/infantrisk--center-resources*, which provides up-to-date and evidence-based information on medication safety during pregnancy and lactation.

The patient should be counseled regarding clothing and other local irritants such as soaps, perfumes/deodorants, and vaginal douching [6]. If using these items, the patient should be counseled to stop using and educated on rationale for discontinuation.

Finally, partner notification is important when treating and managing sexually transmitted infections such as chlamydia, gonorrhea, and trichomoniasis [4]. Clinicians should report to the Department of Health and help identify sex partners and ensure treatment to prevent recurrent infections [25]. Studies

Table 27.2 Recommended treatment guidelines, 2021 [24]

Diagnosis	Treatment	Partner notification required
Bacterial vaginosis	*First line:* Metronidazole 500 mg twice daily for 7 days; clindamycin cream 2% one full applicator intravaginally at bedtime for 7 days or metronidazole (0.75%) gel one full applicator once daily for 5 days *Alternative regimen:* Clindamycin 300 mg orally twice daily for 7 days, clindamycin ovules 100 mg intravaginally at bedtime, tinidazole 2 g oral once daily for 2 days, or tinidazole 1 g once daily for 5 days *Recurrent infection Tx:* Oral metronidazole 400 mg BID x 3 days when beginning and ending menstruation, intravaginal metronidazole 0.75% gel 5-g applicator 2× weekly for 4–6 months *Pregnancy:* Metronidazole 500 mg orally twice daily for 7 days, metronidazole 250 mg orally three times daily for 7 days, clindamycin 300 mg orally twice daily for 7 days	No

Vulvovaginal candidiasis	*First line:* Fluconazole 150 mg orally single dose (not in pregnant women), clotrimazole vaginal suppository 500-mg dose once/200 mg × 3 days/100 mg × 6 days Clotrimazole 1% cream 5 g intravaginally × 7–14 days/2% cream 5 g intravaginally × 3 days; miconazole 100-mg suppository × 7 days/200-mg suppository × 3 days/1200-mg suppository once *Alternative regimen:* Butoconazole 2% cream 5-g intravaginal single dose; econazole vaginal suppository 600 mg once or 200 mg × 3 days; fenticonazole vaginal suppository single 600 mg or 200 mg × 3 days; miconazole 2% intravaginal cream 5-g applicator × 10–14 days or BID × 7 days; oral itraconazole 200 mg two doses total; nystatin vaginal cream 4 g × 14 days *Recurrent infection:* Induction regimen + maintenance Maintenance: Oral fluconazole 100-mg single dose weekly × 6 months; clotrimazole vaginal suppository single 500-mg dose weekly × 6 months; oral itraconazole 400 mg two doses once per month × 6 months *Pregnancy:* Topical azoles preferred once daily × 7 days	No

Table 27.2 (continued)

Trichomonas vaginalis	*First line:* Metronidazole 2 g orally in single dose or metronidazole 400–500 mg twice daily for 5–7 days *Alternative regimen:* Tinidazole 2 g orally in single dose *Recurrent infection:* Repeat standard regimen, confirm partner notification/ treatment, consider drug resistance *Pregnancy:* Metronidazole 2 g orally in single dose	Yes
Chlamydia trachomatis	*First line:* Doxycycline 100 mg twice daily for 7 days Azithromycin 1 g orally in single dose *Alternative regimen:* Levofloxacin 500 mg once daily × 7 days; amoxicillin 500 mg orally TID × 7 days *Recurrent infection:* Repeat standard regimen, confirm partner notification/ treatment *Pregnancy:* Azithromycin 1 g orally in single dose	Yes
Gonorrhea	*First line:* Ceftriaxone 500 mg (for person weighing <150 kg) or 1 g (for person weighing ≥150 kg) IM *Alternative regimen:* Gentamicin 240 mg IM single dose + azithromycin 2 g orally single dose or cefixime 800 mg as single oral dose *Recurrent infection:* Repeat standard regimen, confirm partner notification/ treatment *Pregnancy:* Cefixime 800 mg as single oral dose or ceftriaxone 500 mg IM as single dose	Yes

show that involving index patients in partner notification improves treatment rates [26]. Options include notifying patients for patient-delivered partner therapy or referral. One should clarify partner drug allergies or sensitivities prior to prescribing medications. Another option may be home sampling and testing for partners with educational information on sexually transmitted infections.

Clinical Pearls

- Gathering a good history will assist you in developing an appropriate patient-centered treatment approach.
- In those with multiple episodes of recurrent candidiasis, you may consider testing patient for immunocompromising conditions (i.e., diabetes mellitus) [5].
- Any suspicion for STI or PID should be empirically started on broad-spectrum antibiotics while awaiting culture results in order to reduce the risk of long-term consequences (i.e., scarring, infertility).
- Certain vaginal infections, such as BV and genital HSV, can increase the risk of contracting HIV [1, 12, 27]. STI testing should be offered to sexually active patients as regular screening.
- Use the InfantRiskCenter App© to determine safety of any medication during pregnancy and lactation.
- Review CDC for latest treatment guidelines.

Do Not Miss This!

- Do not assume a patient is not having sex unless you ask, i.e., older patients are having sex and have increase prevalence of STIs.
- Inform and treat partners of patient with STIs.

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Chapter 28
Contraception

Athina Vassilakis and Natasha Natarajan

Introduction

According to the most recent survey done by the Centers for Disease Control and Prevention, about 65% of patients with female organs of reproductive age are currently using contraception [1, 2]. Since certain medical conditions can render pregnancy high risk, contraception can be important to prevent significant health complications [3]. The gamut of contraceptive options developed makes effective, low-risk, and low-hassle choices easily available, but requires appropriate counseling for optimal choice. This chapter reviews key decision-making points, history and physical examination elements needed to guide contraception management, and current contraceptive options available for sexually active patients, including common side effects and contraindications.

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Decision-Making

Contraception visits should start with establishment of absence of pregnancy. When appropriate, emergency contraception options or prenatal management become the focus of the visit. All evaluations should include key medical history and examination to identify any contraindications or precautions for particular modes of contraception due to medical conditions (see Fig. 28.1).

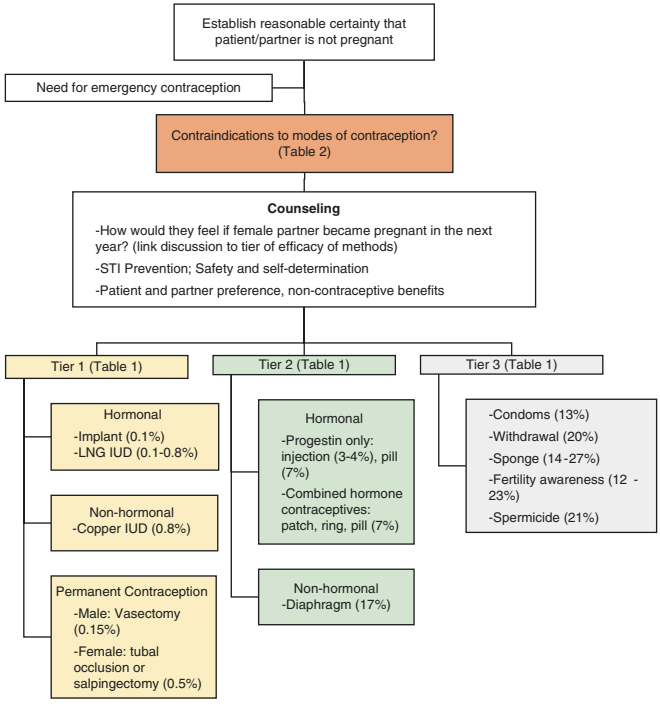

Figure 28.1 Contraception choice (color code links to other tables in the chapter: orange table outlines contraindications; tier levels of efficacy are color coded yellow = tier 1, green = tier 2, gray = tier 3). Percentages are of women becoming pregnant within one year of typical use, which can be significantly higher than failure rates with perfect use of these methods

Contraception discussions are a key opportunity for counseling. Patient ability to refuse sexual encounters or choose contraceptive use, as well as awareness and prevention of sexually transmitted diseases, can allow clinicians to address important behavioral or safety issues.

Additional elements to aid decision-making include obstetric history, reproductive life plans, efficacy level of contraceptive methods, and patient preferences. Patient preference exploration should include noncontraceptive health benefits, interval for thinking about contraception, bleeding patterns, side effects, comfort, practicality of use, and hormonal vs. nonhormonal methods [4]. In order to practice with a reproductive justice framework in mind, all contraceptive options should be discussed with the patient and the patient's choice should be respected. Provider bias such as overemphasizing a single method or recommending different contraceptives to patients of different socioeconomic or cultural backgrounds should be avoided [5]. For adolescents, issues of cognitive development and reliability, high-risk behavior, and confidentiality (including use of parent insurance) need to be considered [6].

Key History and Physical

To establish reasonable certainty that a patient with female organs is not pregnant, ensure there are no current signs and symptoms of pregnancy, and establish *one* of the following: last menstrual period (LMP) within 7 days, no sexual intercourse since LMP, correct and consistent use of a reliable contraception, spontaneous or induced abortion within 7 days, 4 weeks or less postpartum, and at least nearly fully breastfeeding [7, 8]. Alternatively, a pregnancy test can be obtained.

Additional history and examination should focus on safety and self-determination, patient preferences, and possible gynecologic pathology or dysregulation including menstrual cycle problems (dysmenorrhea, menorrhagia, endometriosis),

uterine problems (leiomyomas, other anatomic changes), pelvic inflammatory disease (bimanual and cervical inspection as well as associated symptoms), personal and family history of cancer, smoking, and comorbidities such as hypertension (blood pressure check), HIV status and antiretroviral use, obesity, ischemic heart disease, vasculopathy, pro-thrombotic states (lupus, sickle cell disease, prior thromboses), lactation status, anticonvulsant use, gallbladder disease, migraines, inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease), liver disease, and history of bariatric surgery.

Treatment

The currently available contraceptive methods are summarized in Table 28.1. Table 28.2 presents contraindications or precautions based on the CDC Medical Eligibility Criteria from 2016 [3]. Additional information for select contraceptive methods is presented here, as well as information for emergency contraception and postpartum contraception. Lesnewsky et al. provide detailed information on preventing contraception gaps when switching methods of contraception [11].

Progestin implant is the most efficacious, reversible method of contraception available at this time [12]. A small rod containing etonogestrel is placed subcutaneously in the inner aspect of the nondominant arm. The rod can be felt under the skin and is visible on X-ray imaging. It is approved for 3 years, but may be effective for up to 5 years from the time of placement [6, 8, 13].

Permanent contraception options for patients with female organs include *mini laparotomy, laparoscopy,* or *hysteroscopic tubal occlusion*. Surgical options include clipping, electrocautery, and partial or total salpingectomy. Complications of these procedures are low at 0.9–1.6% [14]. Intraperitoneal adhesions can complicate these procedures. Hysteroscopic tubal occlusion (Essure) was previously allowed for intra-

TABLE 28.1 Contraceptive modes available by efficacy tiers

Tier efficacy	Method	Failure rate[c]	Time to effectiveness	Duration of effectiveness	Possible side effects	General tips/routine follow-up evaluation
Tier 1 effectiveness	Implant	0.1%	7 days[a]	3 years	• Prolonged bleeding: NSAIDs 5–7 days *or* CHC/estrogen for 10–20 days if eligible • Associated with bleeding changes • Breast tenderness, weight gain, headache, nausea, dizziness, and insertion site pain, discoloration, or scarring	• Check for presence of implant after placement. If not palpable, can obtain X-ray imaging; offer other birth control methods
	Vasectomy	0.15%	4 months	Reversible	• Chronic testicular discomfort in 15% overall, 0.9% severe	• Vasovasostomy, when available, can at times return fertility—Subsequent pregnancy rates range 33–64%
	Abdominal/ laparoscopic	0.5%	Immediate	Permanent	• Surgery complication, blood transfusion, infection, ectopic pregnancy, anesthesia complications	• Only postoperative follow-up
	Hysteroscopy	0.5%	3 months	Permanent	• Nickel sensitivity, chronic pain from malposition or expulsion: Remove or reposition device • Bowel injury or obstruction	• Required confirmatory salpingogram in 3 months and then no follow-up. • now removed from the market
	Copper IUD (cu)	0.8%	Immediate	10–12 years	• Prolonged bleeding: NSAIDS for 5–7 days • Pelvic pain: Expulsion, perforation, infection, ectopic pregnancy: Remove device or treat specific etiology • LNG IUD associated with amenorrhea or oligomenorrhea, breast tenderness, acne, headaches, and mood swings	• Bimanual and cervical inspection prior to placement • Can treat pelvic inflammatory disease without removal of device
	LNG IUD	0.1–0.8%	7 days[b]	3–7 years		

(continued)

TABLE 28.1 (continued)

Tier efficacy	Method	Failure rate[c]	Time to effectiveness	Duration of effectiveness	Possible side effects	General tips/routine follow-up evaluation
Tier 2 effectiveness	Injectable progesterone (DMPA)	3–4%	7 days[b]	3 months	• Bleeding: NSAIDs 5–7 days. For heavy or prolonged bleeding CHC or estrogen for 10–20 days (if eligible) • Breast tenderness, weight gain, amenorrhea: If eligible, consider CHC • Headache, nausea, dizziness • Can negatively affect bone mineral density in adolescents	• Check weight • IM injection every 3 months. If delayed for more than 2 weeks, check pregnancy test. If negative, inject and advise backup contraception for 7 days
	Progesterone pill	7%	2 days[a]	Requires continuous use	• Hirsutism, acne, bleeding: If eligible, consider CHC	• Excellent for lactating patients
	Combined hormonal contraceptive Pill, patch, ring	7%	7 days[a]	Requires continuous use	• Headache: If during scheduled bleed, consider extended cycle use • Unscheduled bleeding: Consider triphasic formulation • Decreased libido: Use higher estrogen dose pills • Breast tenderness, mood swings, thrombosis	• Blood pressure check every visit • Patch is changed weekly, ring removed at 3 weeks, pills taken daily • Extended hormone use can decrease side effects • Do not cause weight gain
	Diaphragm	17%	Immediate	Requires continuous use	• Vaginal irritation from spermicide	• Use spermicide with each new encounter while in place and keep for 6 h after last intercourse

Tier 3 effectiveness	Condom	13%	Immediate	Requires continuous use	• Latex allergies	• Prevents sexually transmitted diseases. • Female condoms usually not latex
	Withdrawal	20%	Immediate	Requires continuous use		• Requires partner compliance and body awareness
	Sponge	14–27%	Immediate	24 h	• Vaginal irritation from spermicide	• Effective for 24 h. Keep 6 h post intercourse. • Much less effective in parous women
	Fertility awareness	12–23%	Immediate after period	Requires continuous use		• Various methods available
	Spermicide	21%	Immediate	Requires continuous use	• Vaginal irritation, allergies	• Best used with other methods

[a] If >5 days since LMP
[b] If >7 days since last LMP
[c] Typical use failure rates, which can be significantly different from perfect use failure rates. Created using all references in this chapter

Table 28.2 Category 3 (risks usually outweigh the advantages) or 4 (unacceptable health risk) conditions by type of contraceptive method

Contraceptive method	Contraindications or precautions (method contraindicated or risks likely outweigh the benefits)
Progestin-only implant or pill	Ischemic heart disease[a], liver disease[b], history of stroke[a], SLE with antiphospholipid antibody, anticonvulsant use, rifampin/rifabutin use, history of breast cancer, bariatric surgery causing malabsorption (pill only), unexplained vaginal bleeding (implant only). [a]pill or implant can be initiated for short-term acute benefits, but should not be continued for prolonged periods of time
IUD	Pelvic, uterine, or cervical distortion, cancer, or acute infection[b], unexplained vaginal bleeding with suspicion for serious condition before evaluation, gestational trophoblastic disease with suspicion/evidence of intrauterine disease, complicated solid organ transplantation. *For LNG-IUD only*, current or recent history of breast cancer, liver tumor, or decompensated cirrhosis[b], ischemic heart disease, SLE with antiphospholipid antibody. *For cu-IUD only*, SLE with severe thrombocytopenia or Wilson's disease
Progestin injection	Current or history of breast cancer, liver disease[b], diabetes with complications (vasculopathy, nephropathy, retinopathy, neuropathy), uncontrolled hypertension, vascular disease, ischemic heart disease or high risk for coronary artery disease, rheumatoid arthritis on immunosuppressive therapy, history of stroke, lupus with antiphospholipid antibody or severe thrombocytopenia, unexplained vaginal bleeding with suspected serious condition, breast cancer

Table 28.2 (continued)

Contraceptive method	Contraindications or precautions (method contraindicated or risks likely outweigh the benefits)
Combined hormone contraception (pill, ring, patch)	Hypertension (even controlled), high risk for or current acute thrombosis[b], ischemic heart disease, liver disease[b], high risk for coronary artery disease, peripartum cardiomyopathy, smoking and age > 34 years, history of stroke, diabetes with complications (vasculopathy, nephropathy, retinopathy, neuropathy), vascular disease, complicated valvular heart disease, complicated solid organ transplantation, inflammatory bowel disease (need higher doses of estrogen), antiretroviral therapy or anticonvulsant therapy, rifampin/rifabutin use, breast cancer, symptomatic gallbladder disease, migraines with aura, bariatric surgery causing malabsorption (for pills only), history of cholestasis while on combined oral contraceptives

Adapted and summarized from CDC's Medical Eligibility Criteria for Contraceptive Use, 2016, updated 4/2020

[a]Condition that exposes a woman to increased risk as a result of pregnancy

[b]See original for specific conditions included in this category

tubal fibrosis via hysteroscopic coil placement under local anesthesia but it has now been removed from the market [15].

Intrauterine device (IUD) use is now recommended as a first-line method of contraception, especially for teenagers, nulliparous patients, and patients infected with HIV [16, 17]. Placement is performed in clinic and can involve significant pain. The copper IUD is effective immediately after placement. It should be avoided in Wilson's disease. The levonorgestrel IUD (LNG-IUD) is available in devices for 3 and 5 years of use and may be effective for up to 7 years from the time of placement [18]. It can take up to 7 days to become effective [6, 8, 17].

Progestin-only pills (POPs) are a good option for postpartum and lactating patients and work as well as estrogen-

containing products without safety issues. They are taken daily and become effective within 2 days of use [8].

Combined hormonal contraceptives (CHC) are often used for their noncontraceptive benefits including improvement in acne, menstrual disorders, and menstrual migraines. They are known to increase risk for venous thromboembolism up to ninefold, a risk that is still lower than that of pregnancy and the postpartum period [19, 20]. Typical use involves hormone treatment followed by a hormone-free period during which scheduled bleeding occurs. Extended CHC use involves skipping the hormone-free period for months at a time. It generally induces amenorrhea without any additional health risks. The pill is taken daily. The ring is placed intravaginally and removed at 3 weeks for 3–7 days. If needed, it may be removed for no more than 3 h in any 24-h period. The transdermal patch is changed weekly [6, 8, 21]. For management of missed doses of CHC, readers are referred to the CDC recommendations at http://www.cdc.gov/reproductivehealth/contraception/pdf/recommended-actions-late-missed_508tagged.pdf [8].

Notes on Hormonal Contraceptives: While additional research is needed for clear guidance, current studies show a slight decrease in rate of pregnancy in the first 12 months of trying to conceive in patients who use oral hormonal or IUD contraception in comparison to patients who use condoms or no contraception [22, 23]. Based on current research, there is likely little difference in return to fertility between the various types of hormonal contraception (i.e., oral versus IUD) [23]. Oral contraceptives affect a small increase in cervical cancer risk over time (higher risk with longer use) and a significant decrease in endometrial and colorectal cancer risks [24]. High estrogen dose CHC increases breast cancer risk slightly. Studies assessing risk of low estrogen dose CHC in patients with BRCA mutations show no significant increase in breast cancer incidence from their baseline, but a decreased risk of ovarian cancer [25, 26]. In adolescents, CHCs with greater than 30 micrograms of ethinyl estradiol is preferred over those with less than 30 micrograms in order to optimize bone health [27].

Condoms are the only option to reduce sexually transmitted infections in sexually active people and should be encouraged in addition to all other contraceptive methods for this purpose.

Contraception during the postpartum period is also crucial because patients can start ovulating as early as 21 days after giving birth. Pregnancies that occur less than 18 months apart are at higher risk for preterm delivery, low birth weight, and increased maternal and infant mortality [28]. Postpartum contraception is key to preventing these negative clinical outcomes. During the first 21 days postpartum, there is an increased risk of VTE, making estrogen-containing products such as CHCs unsafe for patients. IUDs, implants, and progestin-only pills are preferred in this initial postpartum time frame. In the interim of 21–42 days postpartum, the recommendation of CHCs depends on the patient's breastfeeding status and presence of risk factors for VTE. Once past 42 days postpartum, CHCs can be prescribed with little to no restriction in both breastfeeding and non-breastfeeding patients [5]. IUDs can be placed both immediately (within 10 min of placental delivery) or in the interval (within 6 weeks postpartum). IUDs placed immediately postpartum are at an increased risk of expulsion compared to IUDs placed in the interval postpartum period [29]. For breastfeeding patients, recent studies have shown no significant effect of the use of progestin implants or IUDs on breast milk production or infant development [30].

Emergency contraception (EC) can prevent unwanted pregnancy after sexual intercourse. The purpose of EC is to prevent ovulation and/or implantation after unprotected sex has occurred; it does not affect already implanted embryos [31]. It is not as effective as routine contraception methods at preventing pregnancy, even though no significant health risks have been associated with its recurrent use. There are three effective options for EC: the copper IUD, ulipristal acetate (UPA), and levonorgestrel. Patients should be counseled not to take higher doses than recommended or mix hormonal methods, as this can decrease efficacy as well as worsen side

effects. The *copper IUD* is the most effective up to 5 days after an encounter, with a failure rate of 0.1%. *UPA* is a one-time, 30-mg progesterone receptor binder pill which inhibits or delays ovulation. It has a failure rate of 0.9–2.1%, which does not decrease over time for up to 5 days. Patients should not restart hormonal contraception for at least 5 days after UPA use and should be counseled about decreased efficacy of progestin-only contraception for up to 2 weeks. *Levonorgestrel* (plan B) is taken as a one-time dose of 1.5 mg and is available over the counter and by prescription. Its failure rate is 0.6% in the first 12 h, but increases to nearly 4% by 72 h [8, 32]. Combination oral contraceptives (two doses of 100 μg of ethinyl estradiol plus 0.50 μg of levonorgestrel taken 12 h apart) can also be used through the Yuzpe method, but they are less efficacious [33]. Side effects of hormonal EC are usually minor and no more frequent than side effects experienced with placebos. They can include headache, abdominal pain, dizziness, fatigue, nausea, dysmenorrhea, and breast tenderness.

Hormonal EC is less efficacious in patients with BMI over 30 (ulipristal 2.6% failure, levonorgestrel 5.6% failure) [34]. It can also have decreased efficacy due to drug interactions, especially with rifampin, griseofulvin, anticonvulsants, St John's wort, and antiretrovirals. Dose doubling has been suggested, however, the efficacy of this practice has not yet been demonstrated [32].

Clinical Pearls

- IUDs and implants are recommended as first-line, reversible modes of contraception for most patients.
- Start by asking patients how they would feel if they became pregnant in the next year.
- Use tiers of effectiveness to present contraceptive methods.
- Postpartum is a crucial time to ensure patients have the right birth control that is both safe and aligns with their reproductive goals.

Do Not Miss This!

- Opportunities to promote discussions about contraception in the clinic—flyers or pamphlets.
- Teenager confidentiality—know state laws, decide whether to use parent insurance.
- Contraception gaps when initiating or switching methods of contraception.
- Offer contraception to patients with serious medical problems to prevent complications.

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Part IX
Genitourinary

Chapter 29
Dysuria

Martin Fried

Introduction

Dysuria refers to a sensation of burning, tingling, or stinging of the urethra that occurs with voiding. This complaint is categorized as an "irritative" symptom—other such symptoms include urinary urgency, frequency, and nocturia. These symptoms are common, with a recent survey demonstrating high prevalence in US and international ambulatory populations [1]. Furthermore, those with more severe urinary complaints have significantly higher rates of comorbid clinical anxiety or depression and lower quality of life. Fortunately, the primary care provider can initiate workup and treatment, and most often, a specialty referral is not needed.

Decision-Making/Differential Diagnosis

The evaluation of dysuria differs depending on the sex of the patient [2]. While most of the etiologies are common, some important disorders are unique to either women or men. As

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such, this review will start with the conditions that may cause dysuria in both sexes before discussing unique aspects of the differential for men and women.

Etiology of Dysuria in both Men and Women

- Inflammatory
  - Infectious

    Urinary tract infections (UTIs): the most common etiology of dysuria [2, 3]

    Urethritis—common in sexually active men and women, usually caused by sexually transmitted infections (see below).

    Cystitis—infection of the bladder, presents with irritative symptoms ± suprapubic pain, cloudy, or malodorous urine.

    Pyelonephritis—upper UTI extending to kidneys, may or may not present with dysuria but will usually have systemic symptoms such as fever, chills, nausea, and vomiting along with tenderness to deep palpation of costovertebral angles. Note that elderly patients with pyelonephritis may not have fever or leukocytosis [3, 4].

  - Sexually transmitted infections (STIs): often present with dysuria and urethral discharge, usually without other irritative symptoms such as urgency and frequency [5].

    Neisseria gonorrhoeae

    Chlamydia trachomatis—serovars D through K, associated with reactive arthritis.

    Herpes simplex virus (HSV)—painful vesicles may cause dysuria in addition to vulvar pruritus, burning, and dyspareunia in women.

    Trichomonas vaginalis—urethritis in men and vulvar irritation with profuse yellow vaginal discharge in women.

- Noninfectious

  Foreign body—typically a migrated ureteral stent or renal stone in transit [2].

  Urethritis (reactive arthritis)—patients with asymmetric oligo-arthritis induced by preceding enteric bacterial infection can develop aseptic urethritis as part of this disease entity.

  Behçet's syndrome—recurrent mucocutaneous ulceration in the scrotum or vulva can produce dysuria.

- Dermatologic

  Irritant/contact dermatitis—usually involving the vulva or urethral meatus, characterized by pruritus and pain with dysuria. Irritants include spermicides, soaps, hygienic products including panty liners and baby wipes, topical medications like antifungals or lubricants, and feces or urine secondary to incontinence.

  Lichen sclerosus—characterized by thin, whitened, wrinkled skin located on the vulva or glans penis in the uncircumcised penis causing pruritus, pain, and dysuria.

• Noninflammatory

- Anatomic

  Urethral stricture/diverticulum—usually presents with bladder outlet obstruction; a history of surgical manipulation is common in these cases [6].

- Drug-related

  Hemorrhagic and nonhemorrhagic cystitis—cyclophosphamide and ifosfamide have highest risk, but other agents are implicated as well [7].

- Neoplastic

  Bladder cancer [8]—typically causes dysuria due to hematuria which can be irritating.

Renal cancer—may present with similar symptoms to those seen with bladder cancer listed above.

– Trauma/iatrogenic [2]

Genitourinary instrumentation or surgery
Foreign body
Pelvic irradiation—causes radiation cystitis months to years after treatment [9]

– Idiopathic

Interstitial cystitis/bladder pain syndrome: typically associated with other pain syndromes such as fibromyalgia and irritable bowel syndrome; classic symptom is lower abdominal discomfort that resolves with urination [1].

Etiologies of Dysuria in Men

- Prostatitis:
  - Acute and chronic bacterial.
  - Chronic prostatitis/chronic pelvic pain syndrome.
  - See Chap. 30 for a full discussion of these entities.
- Epididymitis: most common cause of scrotal pain; consider *Chlamydia* and *Neisseria* infections in younger sexually active men and enteric gram-negative rods in older men or men who engage in insertive anal sex [5].
- Orchitis: aside from mumps, rarely occurs without concomitant epididymitis.
- Benign prostatic hyperplasia (BPH): usually presents with obstructive urinary complaints but is a risk factor for prostatitis and other urinary tract infections [10].
- Prostate cancer: theoretically possible to present with dysuria if urethral obstruction occurs; however, prostate cancer is usually diagnosed in men without specific symptoms.
- Penile cancer: typically presents with skin abnormality or palpable penile lesion but may cause dysuria if ulcer or balanitis is present [11].

Etiologies of Dysuria in Women

- Vulvovaginitis: general category of infectious or inflammatory vaginal changes that cause abnormal discharge with pruritus, burning, dyspareunia, and/or dysuria. The three most common infections are candidiasis, bacterial vaginosis, and trichomoniasis (Fig. 29.1).

- Atrophic vaginitis: a common postmenopausal disorder characterized by dryness, inflammation, and thinning of the vaginal mucosa.
- Endometriosis: urinary tract endometriosis may present with dysuria as well as abdominal pain and menorrhagia.

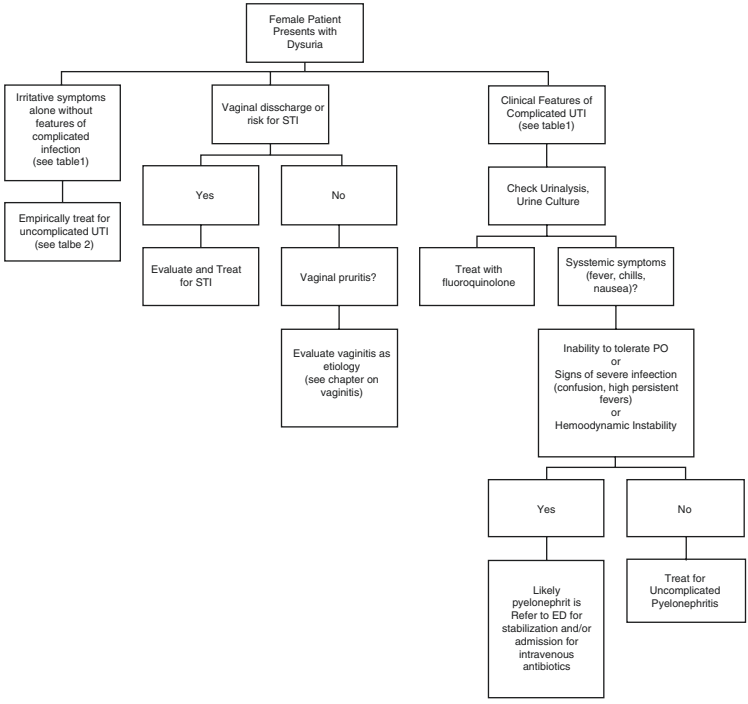

FIGURE 29.1 Approach to the female patient with dysuria

- Vaginal prolapse/pelvic floor disorders: women typically complain of a bulge or vaginal pressure. Irritative or obstructive urinary symptoms are common.
- Vaginal/vulvar cancer: usually presents as vulvar plaque, ulcer, or mass. Vulvar/vaginal bleeding, discharge, or dysuria can also occur but may be suggestive of more advanced disease [2].

Key History and Physical Exam

Because dysuria is a common symptom with a large differential diagnosis, it is important for the clinician to fully characterize the symptom and try to identify the precise location of pain. Many patients who present with dysuria can be treated based on typical findings from the history alone. According to one meta-analysis, the symptom of dysuria in women with urinary frequency without vaginal discharge dramatically increased the likelihood that the patient had a UTI [12] (Table 29.1).

All patients should be asked about bladder outlet obstruction symptoms like hesitancy (difficulty initiating urinary stream) [5]. Urethral discharge and new rashes should be evaluated. Men should be asked about testicular pain and women about cyclical changes or relation of pain to menses

Table 29.1 Features associated with complicated UTIs

Patient characteristics	Medical conditions	Urologic conditions
• Male sex • Pregnancy • Hospital-acquired urinary tract infection • Symptoms for seven or more days prior to seeking care	• Diabetes mellitus • Immunosuppression • Renal failure • Polycystic kidney disease	• Indwelling catheter, stent, nephrostomy tube, or urinary diversion • Recent urologic instrumentation • Renal transplantation • Recurrent or childhood UTIs

which may raise suspicion for endometriosis. Gastrointestinal symptoms like nausea and vomiting may indicate systemic disease or pyelonephritis, while diarrhea or constipation may implicate an adjacent abdominal inflammatory condition such as inflammatory bowel disease or diverticulitis. Musculoskeletal pain may indicate arthritis or tenosynovitis, concerning for reactive arthritis or systemic gonococcal infection, respectively. The past medical history should focus on systemic inflammatory diseases, nephrolithiasis, and exposure to chemotherapy or radiation. A full sexual history should be obtained to evaluate for pattern of intercourse, higher-risk behavior, and current contraception use.

The physical exam should first identify abnormal vital signs like fever or tachycardia that might indicate systemic infection. An abdominal exam should check for abdominal tenderness with specific attention to suprapubic tenderness and bladder distention. Costovertebral tenderness may indicate pyelonephritis, nephrolithiasis, or hydronephrosis. A genital exam, if indicated, should evaluate for rash or discharge. The women's genitourinary exam should evaluate for vulvar and vaginal changes consistent with vaginitis or sclerosus. Bimanual exam is important to check for cervical motion tenderness and discharge. A wet mount can distinguish between candidiasis, bacterial vaginosis, and trichomoniasis, and where that is not available commercial PCR, nucleic acid amplification and rapid antigen tests are becoming widely available.[13] Male genitourinary exam should check for prostate size and texture and testicular swelling or tenderness. A boggy prostate suggests prostatitis; however, use caution when palpating as this may induce bacteremia. Musculoskeletal exam may be indicated if patient has limb complaints to identify joint effusions or tenosynovitis (Fig. 29.2).

Urinalysis and urine culture should not be routinely checked for all patients presenting with dysuria but should be if features of complicated infection are present. If pyelonephritis is being considered, laboratory tests to check renal function and white blood cell count should also be per-

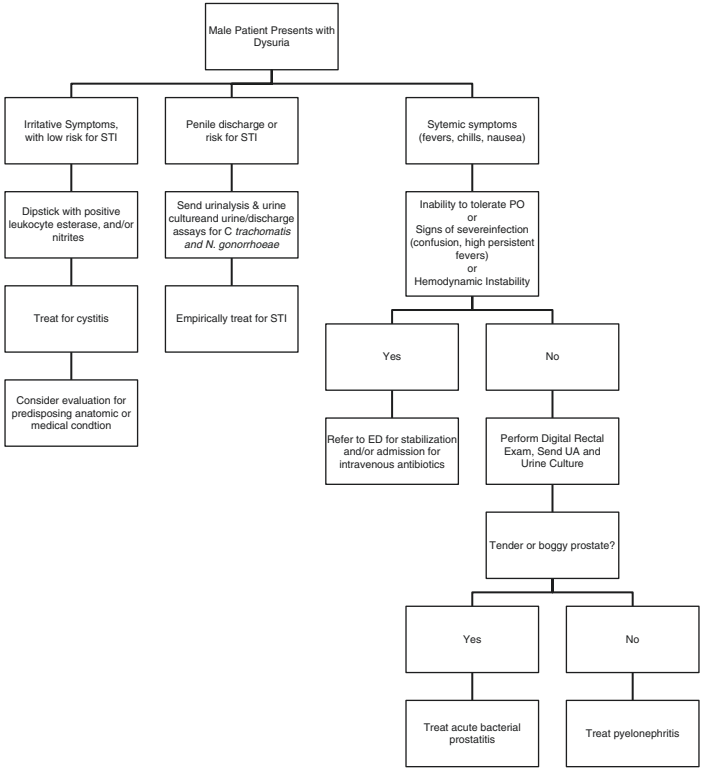

FIGURE 29.2 Approach to the male patient with dysuria

formed. Nucleic acid amplification technique (NAAT)for *Neisseria gonorrhea* and *Chlamydia trachomatis* should be sent from urethral, vaginal, and endocervical sampling or urine if there is risk for an STI. Genital ulcers may be sampled for HSV. Urinalysis and urine culture after prostatic massage should be performed to evaluate for prostatitis. Urine cytology should be checked if bladder cancer is suspected. All patients should be offered human immunodeficiency virus (HIV) testing, especially if other STIs are being considered as an etiology of dysuria.

Treatment

Women who report symptoms typical of uncomplicated cystitis may be treated empirically without further testing. Multiple studies have shown successful empiric treatment of UTIs without adverse outcomes in nonclinical settings such as pharmacies and televisits [14]. IDSA guidelines for treatment of uncomplicated UTIs are listed in Table 29.2 [15]. Local resistance patterns of common enteric organisms should be considered.

Cystitis occurs much less frequently in men than women. For men, treatment options include trimethoprim-sulfamethoxazole, 160/800 mg twice daily, or a fluoroquinolone (dosing per Table 29.2) for a 7–14 day course [16]. While healthy men with a single episode of cystitis that does not recur may not require additional evaluation, most men who experience a UTI should be evaluated for risk factors for UTI. Such predisposing factors include BPH or other urinary tract obstruction, recent instrumentation, or immunocompromising illnesses such as diabetes mellitus. If a urinary tract abnormality is likely, consider referral to a urologic specialist.

If pyelonephritis is suspected, the clinician must first determine if the patient requires transfer to the emergency department for intravenous antibiotics and hydration. Inpatient management is warranted in the setting of severe illness with high fever, pain, inability to maintain oral hydration or medications, when patient is pregnant, or when there is concern about treatment adherence. If deemed safe for outpatient treatment, the following oral agents are preferred per IDSA guidelines [14]:

- Ciprofloxacin, 500 mg twice daily (or 1000 mg extended release, once daily), 7 days.
- Levofloxacin, 750 mg once daily, 5–7 days.
- Trimethoprim-sulfamethoxazole, 160/800 mg twice daily, 14 days.

Table 29.2 Treatment of uncomplicated UTI in women, adapted from 2011 IDSA guidelines [14]

	Drug, dose, duration	Side effects (SEs)	Notes/cautions
First line	Nitrofurantoin, 100 mg twice daily, 5–7 days	Severe SEs are rare but include pulmonary toxicity, hepatotoxicity (cholestasis, hepatitis)	Minimal resistance, minimal ecological adverse effects
			Contraindicated if creatinine clearance < 60
			Avoid if suspicion for early pyelonephritis
	Trimethoprim-sulfamethoxazole, 160/800 mg twice daily, 3 days	Common SEs: Gastrointestinal upset and rash	Avoid if prevalence of resistance is known to exceed 20%
		Severe SEs are rare but include hyperkalemia (type IV renal tubular acidosis), cytopenia, and Stevens-Johnson syndrome	Caution when giving with ACE inhibitor, ARB, or potassium-sparing diuretic
		Causes increase in serum creatinine without affecting true glomerular filtration rate	
	Fosfomycin, 3 g, single dose	Common SEs: Gastrointestinal upset—Nausea, vomiting, and diarrhea may occur	May be less effective than other first-line agents
			Generally more expensive than other first-line agents

Table 29.2 (continued)

	Drug, dose, duration	Side effects (SEs)	Notes/cautions
Second line	Fluoroquinolones	Common SEs: Gastrointestinal upset and neurologic symptoms like headache or dizziness	Should only be used if first-line agent is unavailable or not suitable due to allergy; increasing fluoroquinolone resistance is noted
	• Ciprofloxacin, 500 mg twice daily, 3 days • Levofloxacin, 250 mg once daily, 3 days • Ofloxacin, 200 mg, twice daily, 3 days	Severe SEs are rare but include rashes/allergic reactions, tendonitis, tendon rupture, QT prolongation, and transaminitis	
	Beta-lactams	Common SEs: Diarrhea, IgE-mediated allergies ranging in severity from pruritus flushing (common) to anaphylaxis (rare)	All are less effective than agents listed above and are associated with significant adverse effects
	• Amoxicillin-clavulanate, 500/125 mg twice daily, 3–7 days • Cefpodoxime, 100 mg twice daily, 3–7 days • Cefdinir, 300 mg twice daily, 3–7 days • Cefaclor, 250 every 8 h, 3–7 days	Severe SEs include encephalopathy and Stevens-Johnson syndrome	

Treatment for complicated cystitis may be safe for outpatient therapy. If so, fluoroquinolone-based therapy is appropriate for 5–10 days [17]. Indications for inpatient management are similar for complicated and uncomplicated UTIs, and almost all patients with pyelonephritis who are considered complicated should be treated initially as inpatients.

Urethritis, cervicitis, vaginitis, and bacterial epididymo-orchitis can be treated if the history, physical exam, and/or wet mount is indicative of a sexually transmitted pathogen. *Neisseria gonorrhea* and *Chlamydia trachomatis* are often treated together when the clinician suspects one infection or the other. A 2021 CDC guideline updated the preferred treatment for *C. trachomatis* to oral doxycycline 100 mg twice daily for 7 days. Recommended treatment for *N. gonorrhea* remains a single intramuscular dose of ceftriaxone 500 mg for individuals who weigh <150 kg or 1 g for individuals who weigh ≥150 kg [18]. Epididymitis due to enteric organisms should be treated with a fluoroquinolone such as levofloxacin 500 mg orally once daily for 10 days [18]. If it is unclear if epididymitis is due to an STI or an enteric organism (e.g., in men who participate in insertive anal sex), the patient should be treated with a single intramuscular dose of ceftriaxone 500 mg plus once-daily levofloxacin 500 mg × 10 days [18]. For bacterial vaginosis and trichomoniasis, metronidazole 500 mg twice daily for 7 days is the preferred agent for women, while the former may also be treated with metronidazole gel 0.75%, one full applicator (5 g) once daily for 5 days. [18]. Vaginal candidiasis can be treated with oral or topical antifungals, many of which are over-the-counter in the USA.

The treatment for prostatitis features many of the same agents as for cystitis and pyelonephritis . This is discussed in more detail in Chap. 30 of this manuscript.

Due to the complex differential diagnosis and frequent empiric treatment, patients should be cautioned to return if they meet criteria for complicated infection or if symptoms persist despite treatment. If this occurs and the patient has an unremarkable physical exam, consider interstitial cystitis/

bladder pain syndrome [19], chronic prostatitis/chronic pelvic pain syndrome, overactive bladder, topical irritants, anatomic abnormalities such as urethral stricture or diverticulum, or occult/ongoing STI.

Clinical Pearls

- Dysuria with a convincing history for urinary tract infection—presence of urinary frequency and absence of vaginal discharge—can be treated empirically.
- All patients should be asked about urethral discharge, pruritus, or skin lesions as this may indicate a sexually transmitted infection.
- Men with urinary tract infections may require additional evaluation to determine if a predisposing urinary tract abnormality or medical condition is present.
- A boggy, tender prostate may indicate edema and acute bacterial prostatitis. Use caution as palpation may induce bacteremia.
- If hematuria is present, especially in the absence of white cells on urinalysis, consider renal or bladder malignancy. Check urine cytology, and be sure to follow up after treatment of possible UTI to see if hematuria resolves.

Do Not Miss This!

- Pyelonephritis.
- Sexually transmitted infections and HIV.
- Acute bacterial prostatitis.
- Bladder or renal cancer.

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Chapter 30
Acute Kidney Injury

Valerie Jorge Cabrera

Introduction

Acute kidney injury (AKI) is defined as a deterioration in kidney function, detected by an increase in serum creatinine and decrease in glomerular filtration rate (GFR). Urine output during AKI can be variable, ranging from non-oliguria (>400 mL/day), oliguria (<400 mL/day), to anuria (<100 mL/day). Many classification systems have been used for the diagnosis of AKI, including the RIFLE (Risk, Injury, Failure, Loss of kidney function and End-stage renal disease) criteria, the Acute Kidney Injury Network (AKIN) staging, and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [1–4] (Tables 30.1 and 30.2). In general, AKI is defined as an absolute change in serum creatinine by ≥0.3 mg/dL within 48 h, or an increase in serum creatinine ≥ 1.5 times from baseline within the prior 7 days, or a urine volume < 0.5 mL/kg/h for 6 h [5]. The KDIGO criteria combine RIFLE and AKIN criteria [3] (Table 30.2). Although serum creatinine is a commonly used marker for kidney function, it has several limitations. Gender and muscle mass can influ-

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Table 30.1 RIFLE criteria

	Serum creatinine	GFR	Urine output
Risk	Increased ×1.5	Decreased >25%	<0.5 mL/kg/h × 6 h
Injury	Increased ×2	Decreased >50%	< 0.5 mL/kg/h × 12 h
Failure	Increased ×3 or SCr ≥ 4 mg/dL (with acute rise ≥0.5 mg/dL)	Decreased >75%	<0.3 mL/kg/h × 24 h or anuria × 12 h
Loss	Complete loss of renal function for >4 weeks requiring dialysis		
ESRD	End-stage renal disease (>3 months)		

GFR glomerular filtration rate, *SCr* serum creatinine
Adapted from references [1, 4]

ence the serum creatinine value; lower levels are observed in females, malnourished patients, and those with low muscle mass and liver disease. Some medications (trimethoprim) can affect the tubular secretion of creatinine, resulting in higher creatinine levels despite no change in GFR.

AKI is very common in the hospital setting and is associated with a high risk of mortality and increased risk of chronic kidney disease (CKD) [6]. Community-acquired AKI is similarly associated with increased risk of CKD and risk of death [7]. CKD is defined as a reduced GFR of less than 60 mL/min/1.73 m^2 of body surface area or evidence of kidney damage, such as albuminuria or abnormal findings on renal imaging, present for 3 months or more. Sometimes it is difficult to distinguish whether the elevated serum creatinine is the result of an acute process or represents progression of CKD, especially when a baseline serum creatinine is not available. Sonographic findings of small echogenic kidneys are strongly suggestive of CKD. Other findings, such as ane-

Table 30.2 AKIN and KDIGO staging (Adapted from references [2–4])

AKIN staging			KDIGO staging		
Stage	**Serum creatinine**	**Urine output**	**Stage**	**Serum creatinine**	**Urine output**
1	Increased ×1.5 or ≥0.3 mg/dL from baseline	<0.5 mL/kg/h × 6 h	1	1.5–1.9× baseline or ≥ 0.3 mg/dL	<0.5 mL/kg/h × 6–12 h
2	Increased ×2 from baseline	<0.5 mL/kg/h × 12 h	2	2.0–2.9× baseline	<0.5 mL/kg/h × ≥ 12 h
3	Increased ×3 from baseline or Cr ≥4 mg/dL (with acute rise ≥0.5 mg/dL) or all those patients who receive RRT	<0.3 mL/kg/h × 24 h or anuria ×12 h	3	3.0× baseline or increase to ≥4.0 mg/dL or initiation of RRT or in patients <18 years old, decrease in eGFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/h × ≥24 h or anuria × ≥12 h

eGFR estimated glomerular filtration rate, *RRT* renal replacement therapy

mia, hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism, could be present.

Differential Diagnosis

Traditionally, AKI is classified into prerenal, intrinsic, and postrenal depending on the etiology (Algorithm 1, Fig. 30.1) [8, 9]. However, there can be overlap between categories. For example, prolonged prerenal injury can progress to acute tubular necrosis (ATN).

Prerenal AKI results from compromised renal perfusion due to decreased volume (from gastrointestinal or renal losses), effective volume depletion (seen in patients with con-

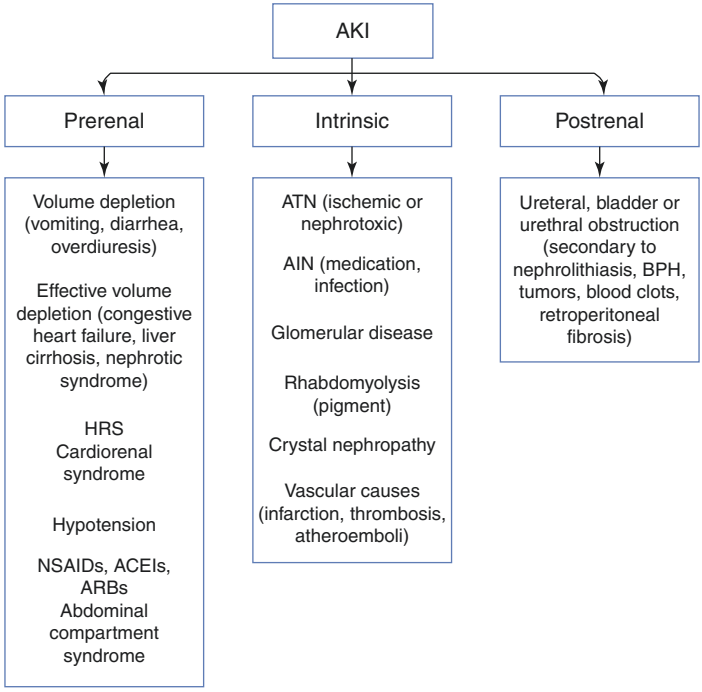

Figure 30.1 Classification of AKI into prerenal, intrinsic, and postrenal

gestive heart failure, liver disease, or nephrotic syndrome), or hypotension related to sepsis. In those with advanced liver disease, hepatorenal syndrome (HRS) is a form of prerenal AKI and is a diagnosis of exclusion. Nonsteroidal anti-inflammatory drugs (NSAIDs) can compromise renal perfusion due to impaired prostaglandin-mediated afferent arteriolar vasodilatation. GFR can also decline in patients taking angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) due to impaired compensatory vasoconstriction of the efferent arteriole in the setting of impaired renal perfusion.

Intrinsic AKI can be categorized according to the compartment involved: tubular, interstitial, glomerular, or vascular.

Acute tubular necrosis results from either prolonged ischemic injury or nephrotoxic injury [10]. Some patients could have features of both prerenal disease and ATN, and volume response can help determine the contribution of the prerenal component. Other forms of tubular injury include myoglobinuria from rhabdomyolysis and hemoglobinuria from hemolysis, which can lead to pigment nephropathy. Crystal deposition can be seen with numerous drugs (acyclovir) and tumor lysis syndrome.

The involvement of the interstitial compartment in acute interstitial nephritis (AIN) can be secondary to medication, infections, and other systemic diseases. The triad of rash, eosinophilia, and fever is not commonly seen (occurs in 5–10% of cases), and eosinophiluria has a low specificity and sensitivity for the diagnosis of AIN [11].

Disorders affecting the glomerular compartment can present in two general patterns, though there can be overlap. A nephritic pattern is characterized by the presence of dysmorphic red blood cells (RBCs) and RBC casts in the urinary sediment, with a variable degree of proteinuria. A nephrotic pattern is associated with proteinuria in the nephrotic range (>3.5 g over 24 h) and an inactive urine sediment.

Diseases that affect the vasculature include small-vessel vasculitis, atheroembolic disease, and diseases associated with

microangiopathic hemolytic anemia (MAHA) and thrombotic microangiopathy (TMA). The latter category includes entities such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), and hypertensive emergencies. Larger-vessel involvement can occur in vascular events such as acute renal infarction and renal vein thrombosis.

Postrenal AKI results from obstruction of both kidneys or ureters (unless the patient has a single functioning kidney) or the bladder outlet. Benign prostate hypertrophy (BPH), nephrolithiasis, or masses are potential culprits. Renal ultrasound (US) is often helpful, but in retroperitoneal fibrosis and acute obstruction (<48 h), hydronephrosis can be absent (Fig. 30.1).

Key History and Physical Exam

A detailed history focused on certain symptoms is essential (Fig. 30.2) [8]. The clinician should inquire about symptoms suggestive of volume loss (vomiting, diarrhea, and excessive diuresis), weight loss, and decreased oral intake. Urinary symptoms such as difficulty with urination, decreased urine

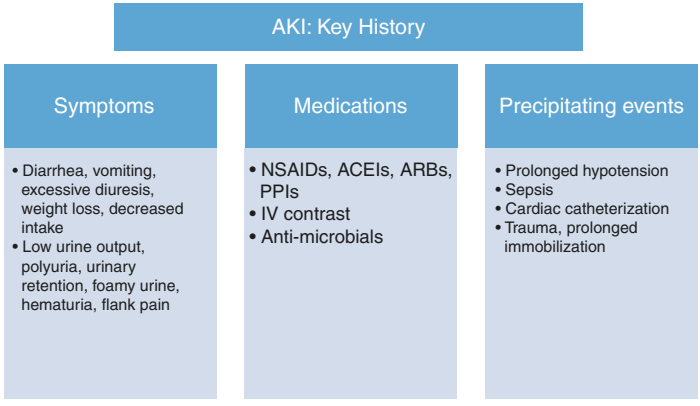

Figure 30.2 Key elements in the history taking of a patient with AKI

output, hematuria, and foamy urine should be reviewed. A review of systems with other associated symptoms, including flank pain, fever, or chills should be completed. A thorough review of the medication list, documenting use of over-the-counter medications, supplements, NSAIDs, proton pump inhibitors (PPIs), and recent medications taken (antibiotics), is of great importance. In the hospital setting, review of recent events (hypotension, recent cardiac catheterization, or contrast administration) could be revealing and point to the etiology of AKI.

Physical examination (Fig. 30.3) should include assessment of vital signs and weight. The physician should evaluate for the presence of exam findings suggestive of volume overload (neck vein distention, S3, crackles, and peripheral edema) or volume depletion (orthostasis, dry mucous membranes, and decreased skin turgor). A thorough exam should evaluate for flank tenderness and for the presence of ascites and suprapubic distention. Signs of uremia (pericardial rub, confusion, asterixis) should be evaluated carefully. The clinician should also conduct a thorough skin examination, looking for rash, petechiae, purpura, or skin color changes, such as jaundice. In those with history of trauma or recent surgery, the clinician should assess for presence of compartment syndrome on physical exam.

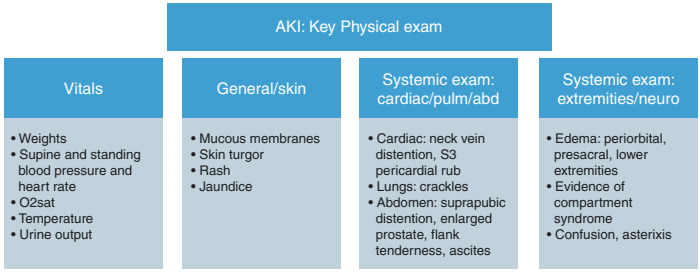

Figure 30.3 Key elements in the physical examination of a patient with AKI

Decision-Making/Treatment

The initial workup of AKI involves the evaluation of a urinalysis (UA) to assess the urine specific gravity, pH, and the presence of proteinuria, hematuria, and pyuria (Algorithm 2, Fig. 30.4) [8]. The quantification of urine protein or albumin can be obtained with measurement of a random or "spot" protein-to-creatinine ratio or albumin-to-creatinine ratio. Evaluation of the urine sediment is crucial [12]. The presence of casts and cells can point toward the etiology of kidney injury: granular/muddy brown casts and renal tubular epithelial cell casts are seen in ATN and pigmented casts in rhabdomyolysis and hemolysis, and white blood cell (WBC) casts are suggestive of AIN or pyelonephritis. Hyaline casts are nonspecific and can be seen in patients with prerenal AKI or those with a concentrated urine. The presence of dysmorphic RBCs and RBC casts is suggestive of a glomerulonephritis, while isomorphic RBCs are typically seen in patients with nephrolithiasis and tumors.

The fractional excretion of sodium (FENa), calculated as FENa = (urinary sodium/plasma sodium) × (plasma creatinine/urinary creatinine) × 100, is typically low (<1%) in AKI from prerenal etiologies and high (>2%) in the setting of other etiologies of AKI [13]. The fractional excretion of urea (FeUrea), calculated as FeUrea = (urinary urea/plasma urea) × (plasma creatinine/urinary creatinine) × 100, is more useful in those patients that have been taking diuretics. A value <35% is suggestive of prerenal azotemia, while >50% suggests ATN. However these urine chemistries suffer from low sensitivity and specificity [14], particularly in those patients with underlying CKD.

A renal US is valuable when obstruction is suspected, especially if the patient has a large postvoid residual (defined as >100 mL of urine) or cancers that involve the retroperitoneum.

Depending on the history, physical, radiographic, and urine findings, particularly if there is a suspicion for a nephritic or nephrotic pattern, serologic testing is recom-

mended to further characterize the etiology of kidney disease. Lastly, kidney biopsy may be necessary if the cause of AKI remains unclear (Fig. 30.4).

For patients who are in a steady state and/or CKD is suspected, a GFR can be estimated. Common methods include measurement of the creatinine clearance and the use of estimation equations. The accuracy of creatinine clearance can be limited by an incomplete urine collection and the rate of creatinine secretion, which can be increased in patients with CKD. There are different equations to estimate GFR, including the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the MDRD study equation, and the Cockcroft-Gault equation. The CKD-EPI equation was developed in 2009 and revised in 2021without a term for race [15].

The treatment of AKI is directed toward correcting the underlying etiology and providing supportive measures. Other important steps include the following:

- Prompt relief of obstruction and monitoring for postobstructive diuresis.
- Avoiding further nephrotoxins is essential. Medications such as NSAIDs should be avoided.
- Medications should be dosed for the patient's renal function, according to the presumed GFR.
- Assess for drugs that are renally cleared and can produce adverse effects if they accumulate in AKI (such as metformin, gabapentin, and morphine).
- Avoidance of hypotension is recommended, as hemodynamic changes can precipitate or complicate AKI.
- Hydration with intravenous isotonic fluids (IVFs) can be used if the clinical scenario is suggestive of volume depletion, but care should be undertaken if the patient is oliguric or anuric, as volume overload is a common complication.
- Diuretics can be used if the patient has evidence of volume overload [16].

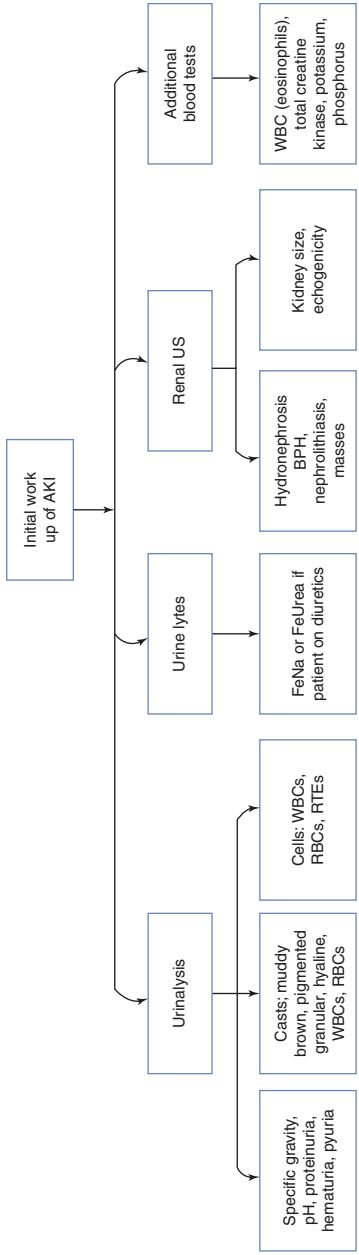

FIGURE 30.4 Initial laboratory and radiologic testing in a patient with AKI

- Patients with AKI can benefit from dietary restrictions on potassium, phosphorus, sodium, and fluid intake, depending on the clinical scenario.
- The clinician should monitor carefully for indications that would prompt dialysis, such as refractory hyperkalemia, acidosis, volume overload, uremic encephalopathy, and uremic pericarditis.

Clinical Pearls

- A thorough history and physical examination are essential in patients with AKI.
- ACEIs and ARBs can cause an increase in serum creatinine level. A change of 20–30% is acceptable. In patients with a higher increase in serum creatinine, hypotension, or significant hyperkalemia (serum potassium > 5.5 mEq/L), the ACEI or ARB should be discontinued.
- Use phosphate-containing bowel preparations with caution in patients with CKD, as acute phosphate nephropathy can occur.
- For prevention of contrast-induced AKI, minimize contrast volume and provide isotonic fluid when possible. Dialysis has no role in prevention of contrast-induced AKI. In those with end-stage renal disease (ESRD) already on dialysis, removal of contrast on the next scheduled dialysis session is appropriate.
- Contrast studies with gadolinium should be employed cautiously in patients with GFR < 30 mL/min due to increased risk of nephrogenic systemic fibrosis (NSF).
- Referral to a nephrologist is advisable for patients with established stage 3 CKD (GFR < 60 mL/min/1.73 m^2) and recommended for those with stage 4 CKD (GFR < 30 mL/min/1.73 m^2).
- In patients with CKD, the use of peripherally inserted central catheters (PICC) and subclavian catheters should be avoided, as the resulting central vein stenosis makes access difficult for those requiring dialysis in the future.

Do Not Miss This!

- Watch for indications for dialysis: refractory hyperkalemia/severe acidosis, uremic encephalopathy/pericarditis, and refractory volume overload.
- Review the medications the patient has been taking, and do not forget to check for over-the-counter medications. Adjust all medications for the patient's renal function.
- Evaluate for urinary obstruction. It is a highly reversible cause of AKI when detected and treated early.
- Trimethoprim is associated with a spurious increase in serum creatinine without change in GFR due to blockage of tubular secretion of creatinine. True hyperkalemia can occur due to blockage of the epithelial sodium channel in the distal nephron.
- History of recent trauma, use of statins, and dark urine are suggestive of rhabdomyolysis: check a total creatine kinase level.

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Chapter 31
Prostate Problems

Martin Fried

Introduction

Prostate problems can be divided into three general categories: (1) prostatitis, (2) benign prostatic hyperplasia (BPH), and (3) prostate cancer.

Prostatitis

Prostatitis is a common problem worldwide with prevalence of prostatitis-like symptoms ranging between 2% and 9.7% among community-based healthy populations [1]. The predominant symptom of prostatitis is abdominal or pelvic pain. The National Institutes of Health classification of prostatitis includes four distinct syndromes (Table 31.1) [2]. Prostatitis type IV—asymptomatic inflammatory prostatitis—is defined as evidence of inflammation on prostate biopsy or infertility workup in a patient without symptoms. This entity will not be discussed further as it has not been sufficiently studied to determine natural history or need for treatment.

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Table 31.1 NIH classification of prostatitis (1999)

• Acute bacterial prostatitis
• Chronic bacterial prostatitis
• Chronic prostatitis/chronic pelvic pain syndrome
• Inflammatory
• Noninflammatory
• Asymptomatic inflammatory prostatitis

Decision-Making/Differential Diagnosis

Acute Bacterial Prostatitis

Patients with acute bacterial prostatitis will present with relatively sudden-onset urologic symptoms including irritative (dysuria, frequency, urgency) and/or obstructive symptoms [3]. Risk factors include BPH, recent genitourinary infections, high-risk sexual behavior or history of sexually transmitted infection, and procedural or surgical prostate manipulation such as urethral catheterization or transrectal biopsy. Physical exam and laboratory analysis will provide evidence of bacterial infection of the prostate.

Other genitourinary tract infections like cystitis and urethritis can present similarly, and the differential diagnosis can be broad. Among gastrointestinal conditions, diverticulitis and proctitis can present with lower abdominal pain and fevers and should be considered if urinary symptoms are not prominent. Finally, clinicians should consider prostatic abscess if fevers or other symptoms persist despite appropriate antibiotics.

Chronic Bacterial Prostatitis

Some patients with acute bacterial prostatitis will continue to have chronic or recurrent urogenital symptoms with evidence of bacterial infection of the prostate [4]. When symptoms

have lasted for 3 months or longer with identical culture results, the disease is classified as chronic bacterial prostatitis. Risk factors for this entity are unclear, but retrospective analyses have suggested prior manipulation of the urinary tract, and higher prostate volumes may be risk factors for chronic bacterial prostatitis [5].

Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

The NIH separates this entity into an "inflammatory" and "noninflammatory" category [2]. Presence of inflammatory cells expressed in prostatic secretions, post-prostate massage urine, or seminal fluid distinguishes the inflammatory category. In addition to pain and lower urinary tract symptoms (LUTS), CP/CPPS has a much higher incidence of sexual dysfunction including erectile dysfunction and ejaculatory pain than other etiologies of prostatitis [6].

Other Chronic Etiologies

Interstitial cystitis/bladder pain syndrome is a complex disorder characterized by chronic bladder discomfort. More common in women than men, the pain or pressure is usually relieved by voiding. It commonly coexists with other chronic pain syndromes including fibromyalgia and irritable bowel syndrome [7].

Bladder cancer most commonly presents with painless hematuria. However, voiding symptoms or abdominal pain may be present in carcinoma in situ or locally advanced disease, respectively (Fig. 31.1).

Key History and Physical Exam

The chronicity and severity of symptoms is the most important information to gather initially. Patients with acute bacterial prostatitis may require inpatient admission if there is

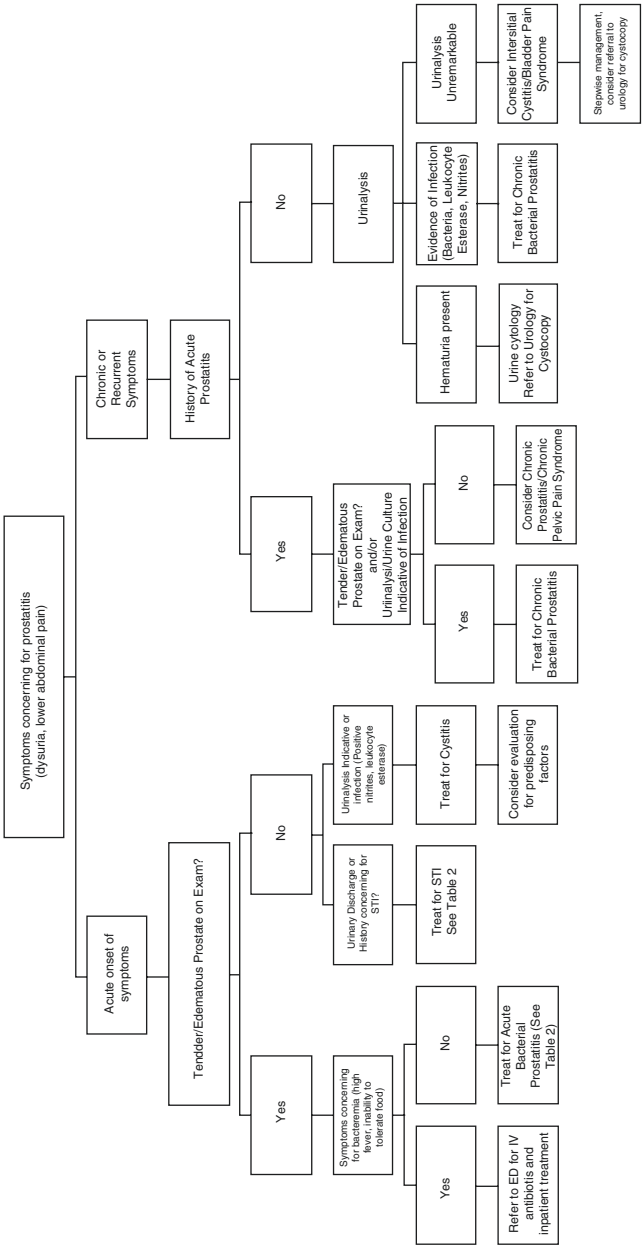

FIGURE 31.1 Approach to patient with symptoms concerning prostatitis

suspicion for bacteremia (persistent fevers or chills) or if they cannot tolerate oral medications. Failed outpatient management is also an indication for admission [3].

Most patients with prostatitis can be treated as outpatients. If so, a full characterization of urinary complaints with attention to irritative or obstructive symptomatology is important to both determine risk factors and comorbid conditions such as BPH. Clinicians should also take a full sexual history to determine the need to treat for sexually transmitted infections and should also evaluate for erectile dysfunction or pain with erections. Gastrointestinal symptoms should be evaluated, including constipation, diarrhea, and tenesmus if diverticulitis or proctitis is suspected. A medical history significant for similar symptoms in the past may suggest chronic bacterial prostatitis, and history of sexually transmitted infections or urologic procedures is also relevant [3].

The physical exam of a patient with suspected prostatitis should include both a full genitourinary (GU) exam and digital rectal exam (DRE). The GU exam should check for phimosis which increases the risk for bacterial prostatitis as well as ulcers, vesicles, or discharge that may suggest an STI. The DRE should assess for tenderness, edema, and size of the prostate. If acute bacterial prostatitis is suspected, DRE should be done gently or avoided as vigorous prostatic massage can induce bacteremia. Patients with acute or chronic bacterial prostatitis typically have the classic "boggy" or edematous prostate. This should be absent in CP/CPPS. If obstructive symptoms predominate, a post-void bladder residual volume may be assessed by ultrasonography.

The laboratory evaluation of prostatitis includes a urinalysis and urine culture in all patients. The urine collected should be midstream as abnormalities of early-stream urine reflect urethral meatus pathology, while abnormal findings in late-stream urine reflect bladder pathology. Prostatic fluid sampling, performed by collecting a urinalysis and culture after prostatic massage, may be useful especially when evaluating for chronic prostatitis. Serum complete blood count and creatinine level should be checked for leukocytosis or renal

insufficiency indicative of systemic infection or hydronephrosis, respectively. Additionally, a human immunodeficiency virus (HIV) screening test should be offered to all patients in addition to *Neisseria gonorrhoeae* and *Chlamydia trachomatis* PCR testing if indicated. Urine cytology may be considered if hematuria and risk factors for bladder cancer (smoking, age > 40 years) are present. Serum levels of prostate-specific antigen (PSA) will likely be elevated in the setting of prostatitis. This may be useful when entertaining other organ systems in the differential diagnoses. If prostate cancer screening is planned, it should be deferred until 1 month after the symptoms of prostatitis are completely resolved.

Treatment

Antibiotics are the mainstay of therapy for acute and chronic bacterial prostatitis. Both entities can be treated empirically while awaiting culture data. Table 31.2 lists optimal choices for empiric treatment of bacterial prostatitis [8]. Chronic or recurrent bacterial prostatitis should be treated with one of these agents for at least 6 weeks [9]. Culture-directed therapy should commence once that data is available. In addition to antibiotics, evaluation into predisposing behavioral or anatomic risk factors should be considered and may require assistance from urologic specialists.

Table 31.2 Empiric treatment of acute bacterial prostatitis (all courses 10 days unless otherwise specified) [8]

- Ciprofloxacin 500 mg every 12 h
- Levofloxacin 500 mg once daily
- Trimethoprim-sulfamethoxazole: One double-strength tab orally every 12 h

If patient has risk factors for STIs:

- Ceftriaxone 250 mg intramuscularly × one dose
- Doxycycline 100 mg twice daily

The treatment of CP/CPPS is far more challenging. The NIH chronic prostatitis symptoms index (NIH-CSPI) is a useful tool for tracking response to therapy [10]. Alpha-adrenergic antagonists, antibiotics, and 5-alpha-reductase inhibitors are the three main classes of therapies with good evidence of efficacy [11]. In one study the combination of tamsulosin 0.4 mg daily and ciprofloxacin 500 mg twice daily for 6 weeks had the best response compared to placebo [12]. Given the high prevalence of comorbid psychosocial problems in this group of patients, referral for cognitive behavioral counseling is a reasonable option. Acupuncture and physical therapy are alternative options that may be helpful as well.

Benign Prostatic Hyperplasia

BPH is characterized by lower urinary tract symptoms (LUTS) such as urinary hesitancy (difficulty initiating micturition), incomplete voiding, or weak stream. BPH is uncommon in men younger than 40 years of age, but histologic evidence of the condition is near universal in men over 80 years of age [13].

Decision-Making/Differential Diagnosis

It is important to recognize that LUTS are not specific for BPH, and the presence of these symptoms may indicate several different disorders [14]:

- Overactive bladder (OAB): Will have a predominance of storage symptoms without evidence of outlet obstruction. However, longstanding BPH may cause bladder remodeling that increases risk for developing OAB with concomitant outlet obstruction.
- Sometimes subcategorized into neurogenic and non-neurogenic. Prior stroke, Parkinson's disease, multiple sclerosis, or spinal cord injury may lead to neurogenic OAB.

- Urethral stricture (including bladder neck obstruction or contracture): Usually patients will have a history of urethral trauma, urethral instrumentation, or urethritis.
- Bladder calculi or bladder carcinoma: These may present with gross hematuria or pain in the bladder region in addition to LUTS.
- Prostatitis: This is characterized by lower abdominal/pelvic pain usually with irritative symptoms. See above.
- Prostate carcinoma: This is often asymptomatic; consider screening with PSA.
- Medications causing LUTS: These may include antidepressants, diuretics, bronchodilators, and antihistamines.

Key History and Physical Exam

When men present with LUTS, the clinician should first evaluate the severity of the symptoms. This can be done by using a validated tool such as the International Prostate Symptom Score (IPSS) [15]. When a patient complains of obstructive urinary symptoms, it is important to identify which of the following categories are present:

- Storage symptoms: urgency, daytime frequency, nocturia, and urgency incontinence (defined as involuntary leakage accompanied or preceded by urgency).
- Voiding symptoms: slow stream, flow that stops and starts (intermittency), straining to void, terminal dribble, or dysuria.
- Post-micturition symptoms such as sensation of incomplete emptying and post-micturition dribble (occurring after leaving the toilet as opposed to the terminal dribble).

The physical exam should include a GU exam as well as DRE to assess the size, texture, and presence of nodularity concerning prostate cancer. If OAB is suspected, a focused neurologic exam is also indicated. The laboratory workup could include urinalysis and urine culture if prostatitis is being considered. The decision to send a PSA is discussed below (Fig. 31.2).

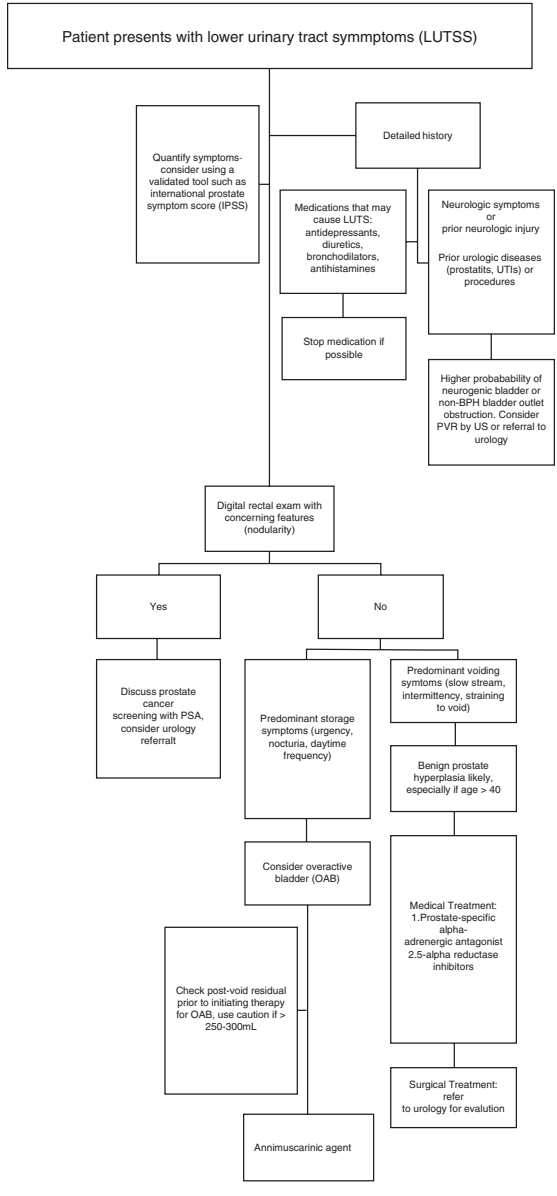

FIGURE 31.2 Approach to patient with lower urinary tract symptoms

Treatment

Behavioral modification is the first step regardless of symptom severity [16]. Such interventions include avoiding fluids prior to bedtime and reducing natural diuretics like caffeine and alcohol. Classifying a patient's symptoms has important therapeutic implications. Those patients who have storage symptoms may benefit from prostate-specific alpha blockers such as tamsulosin with or without the addition of 5-alpha-reducase inhibitors such as finasteride. The addition of an antimuscarinic agent may be useful if the patient has OAB [17]. Oxybutynin and tolterodine are examples of such agents and, as a class, have significant side effects such as dry mouth, blurry vision, and drowsiness that often limit the patient's tolerability. Peripherally acting antimuscarinics, e.g., darifenacin, theoretically have fewer side effects. It is prudent to ensure that patients do not have elevated post-void residual volumes (greater than 300 mL) prior to initiating an antimuscarinic agent. Herbal medications like saw palmetto have traditionally been used to treat BPH. However, a recent Cochrane meta-analysis found that saw palmetto was not more effective than placebo in reducing LUTS in men with BPH [18].

Surgical treatment remains an option in the setting of medication failure or intolerance. At this point referral to a urologist is indicated.

Prostate Cancer

Prostate cancer is the most commonly diagnosed non-skin cancer in men with an expected 248,530 new cases in 2021 [19]. The majority of cases are diagnosed in men older than 60 years. However, with prostate-specific antigen (PSA) screening rates declining, we may soon see a shift in the epidemiology of this disease. This continues to be an area of controversy and current guidelines vary dramatically among various organizations for both screening and treatment of prostate cancer.

Decision-Making/Differential Diagnosis

The differential diagnosis for prostate cancer includes the other diagnoses discussed in this chapter. However, the decision to screen for prostate cancer using serum PSA levels is among the most complex and controversial issues in medicine. Data from large, well-designed randomized trials are inconsistent in mortality reduction, and those that do support screening suggest a small absolute risk reduction [20, 21]. The harms from screening are also significant and include risk of infectious complications of biopsy, overdiagnosis of cancers that would never become clinically significant, and morbidity from prostate cancer treatment including postoperative incontinence, sexual dysfunction, and bowel problems [22]. However, recent longer-term follow-up of multiple prostate cancer screening trials has increased confidence that PSA-based screening does increase detection of early disease and reduce advanced disease in some men. As such the US Preventive Services Task Force (USPSTF), the panel which makes evidence-based recommendations for various screening tests, has upgraded PSA screening from a grade D, recommending against the service, to a grade C for men ages 55–69 years [23]. This also reflects increasing use of active surveillance of low-risk prostate cancer. Published in 2021, the National Comprehensive Cancer Network's Prostate Cancer Early Detection algorithm suggests initiating screening even earlier: Initiate PSA at age 45 years for average-risk patients and 40 years for those with African ancestry or concerning family history, with follow-up intervals based on the results of the initial PSA result [24]. The American Urological Association (AUA) 2013 consensus statement remains the most up-to-date guidelines from this group, reviewed and confirmed in 2018, and recommends shared decision-making for men aged 55–69 years and to avoid routine screening with PSA outside of this age group [25].

Key History and Physical Exam

Risk factors for prostate cancer may influence a patient's decision about whether to undergo screening for the disease. The most important risk factor for prostate cancer is age [26]. Outside of this, prostate cancer is more common in Black than White or Hispanic men, and the age of onset is earlier in African-Americans than comparative groups [27]. An affected first-degree relative is also associated with an increased risk of prostate cancer.

Although once thought to be a reliable screening tool, the DRE is not recommended to evaluate for prostate cancer. However, incidentally found nodularity, asymmetry, or induration on DRE may influence the decision to use PSA as a screening tool for prostate cancer.

Treatment

Surgery and radiation therapy have been the treatments most commonly offered for men diagnosed with prostate cancer. However, a recently published study that compared active monitoring, radical prostatectomy, and external beam radiotherapy suggests that prostate-cancer-specific mortality is low and not significantly affected by treatment [28].

Clinical Pearls

- The NIH prostatitis classification scheme is useful to categorize men who present with lower abdominal pain and irritative or obstructive urinary complaints.
- If acute bacterial prostatitis is being considered, use caution with digital rectal exam as prostatic massage may induce bacteremia.
- Chronic prostatitis/chronic pelvic pain syndrome is a diagnosis of exclusion and may require a long course of antibiotic and a prostate-specific alpha-antagonist.
- Benign prostatic hyperplasia is a common entity among older men, but clinicians should appreciate that lower uri-

nary tract symptoms may indicate other etiologies like overactive bladder.
- Prostate cancer screening with serum PSA levels is falling out of favor among many professional organizations. Be sure that patients are fully informed about the strengths and weaknesses of the test.

Do Not Miss This!
- Acute bacterial prostatitis can present with lower abdominal and pelvic pain.
- Prostatic abscess may be the problem in men who do not respond to initial course of antibiotics.
- Sexually transmitted infections like *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and HIV can occur in older men and should always be part of the differential diagnosis.
- Remember that there are causes of LUTS besides BPH: overactive bladder, urethral stricture, or bladder carcinoma.

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Part X
Gastroenterologic

Chapter 32
Abdominal Pain

Rosemarie L. Conigliaro and Sreekala Raghavan

Introduction

Abdominal pain is one of the most common presenting complaints in outpatient medicine and one of the most challenging. The etiology of abdominal pain may be related to a structural abnormality of any of the abdominal organs, part of a more systemic process (e.g., vascular or metabolic), or referred pain from a non-abdominal structure (e.g., myocardial ischemia, pleuritis). The initial assessment of abdominal pain involves an assessment of the severity and the timing—acute versus chronic [1]. There is no clear delineation for when abdominal pain is considered chronic; processes which are long-standing yet intermittent, ongoing for months or years, and/or unchanged and not progressive may safely be

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considered chronic. In the primary care setting, in about one-third of patients with abdominal pain, the underlying cause is not identified [2]. However, any patient with severe abdominal pain and/or pain of recent onset requires an immediate and thorough evaluation.

Key History and Physical Exam

The history is key for the diagnosis of acute abdominal pain; the most important is the chronological sequence of symptoms. Other important information includes a complete description of the pain including localization, characterization, precipitating and relieving factors, and previous episodes [3]. Additional history should include previous surgeries, family history, constitutional symptoms, and extraintestinal manifestations. Finally, a complete medication history, including all over-the-counter medications and supplements, should be obtained, as well as an evaluation for known systemic diseases and risk factors for such (e.g., cardiac or pulmonary).

A careful physical exam is essential to assess the acuity and location of the pain and if the pain is made worse with any pressure changes in the abdomen, such as with palpation, coughing, or movement, which would imply peritoneal irritation. The presence or quality of bowel sounds does not significantly aid in diagnosis, although a completely quiet abdomen is consistent with severe peritonitis. Overall, the sensitivity and specificity of the physical exam is poor for diagnosing a cause of abdominal pain, especially in the setting of chronic abdominal pain [3]. Acute abdominal symptoms may be related to a complete or partial obstruction of a hollow viscus, with pain that comes in waves, referred to as colicky pain. Visceral pain, which may be related to a gastrointestinal, biliary, genitourinary, or gynecologic process, is characteristically dull and may be less well localized than peritoneal pain [3] and thus more difficult to evaluate.

Additional physical examination findings which may be helpful include checking for ascites, vascular bruits, organomegaly or other masses, Murphy's sign (inspiratory arrest due to pain from deep palpation below the right costal margin), Carnett's sign (described below), costovertebral angle tenderness, and palpation of the abdominal wall and muscles. All patients reporting acute abdominal pain should underdo digital rectal examination with testing for occult blood, and pelvic examination should be performed in female patients to assess for pelvic pathology when appropriate.

Laboratory studies which may help determine a specific etiology include urinalysis, serum bilirubin, transaminase and lipase levels, and pregnancy testing. Abnormalities of the leukocyte count, amylase level, electrolytes, and renal function may indicate severity of illness or degree of hydration without elucidating any specific diagnosis. Imaging should be focused and thoughtful and based on clearly delineated differential diagnoses.

For acute abdominal pain, delineating the pain as primarily originating from one of the four abdominal quadrants (right upper, right lower, left upper, left lower) or nonlocalized pain allows for an initial differential diagnosis (see Fig. 32.1). Physical examination in patients with abdominal pain has low specificity and low sensitivity for identifying specific etiologies, and few laboratory tests are diagnostic; thus, the differentiation of causes of acute abdominal pain may require targeted imaging studies [1]. Plain radiography may be useful in cases of suspected bowel obstruction, nephrolithiasis, or foreign body ingestion. More commonly employed are abdominal computerized tomography (CT), usually with contrast, or ultrasound, or no imaging for diagnoses made with alternative testing. CT scan may detect a cause of abdominal pain in approximately half of patients; higher yield of CT occurs in the pediatric setting, in patients with leukocytosis, and with identifying a specified diagnosis prior to obtaining a CT [4]. In the interest of decreasing radiation exposure, magnetic resonance imaging (MRI) and

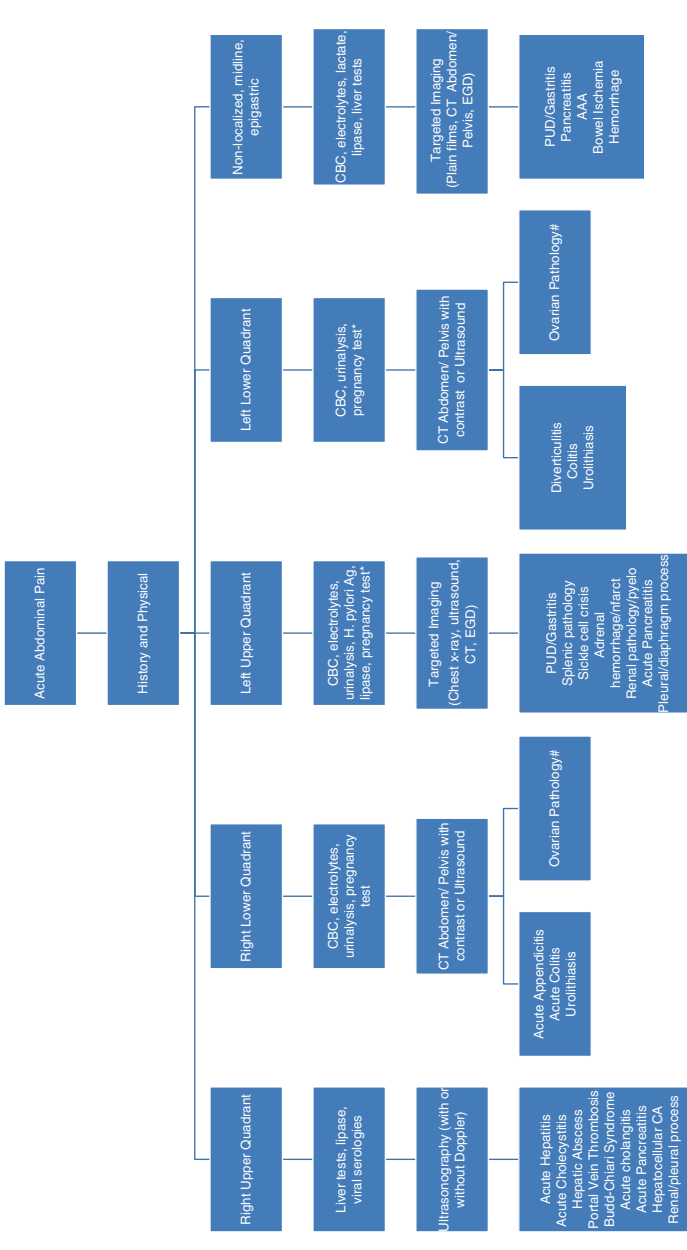

FIGURE 32.1 Acute abdominal pain evaluation. *Substitute ultrasound or MRI for pregnant patients with acute abdominal pain requiring imaging. #Denotes ovarian torsion, ovarian cyst, or ectopic pregnancy. Pelvic inflammatory disease may be diagnosed by pelvic examination and does not require imaging

ultrasound have been utilized more, reserving CT only for nondiagnostic studies in selected cases.

Chronic abdominal pain requires a different approach (see Fig. 32.2). The diagnosis of functional disease relies heavily on the history because there are no characteristic physical or laboratory findings to aid in diagnosis. Functional conditions may be identified by their symptomatology, which is usually vague and insidious, and lack of alarm symptoms (e.g., family history of gastrointestinal cancer, onset after the age of 55 years, weight loss, dysphagia, palpable mass, or evidence of bleeding) [5]. For abdominal wall pain, diagnosis is made by physical exam; a positive Carnett test, where there is an increase of palpable pain with tensing of the abdominal wall muscles, is highly sensitive and specific [6].

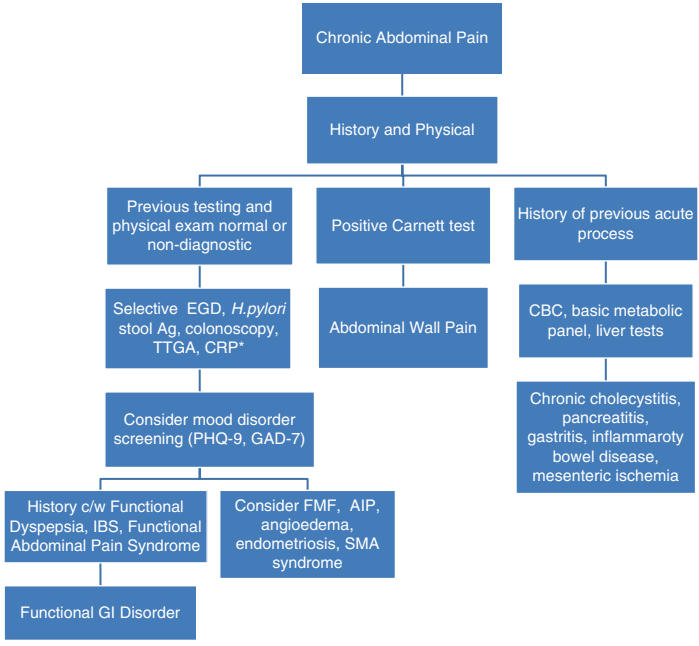

FIGURE 32.2 Chronic abdominal pain evaluation. *Based on symptoms and/or to rule out alternative disorders

Decision-Making/Differential Diagnosis

Patients with acute right upper quadrant (RUQ) pain with an enlarged, tender liver on physical examination, jaundice, and elevated transaminase levels likely have acute hepatitis, either viral or toxin (e.g., drug or alcohol) induced. Pain may be accompanied by nausea, anorexia, and fatigue. These patients do not require further imaging; appropriate serologic tests can discern the underlying etiology, most commonly hepatitis A, B, and C, Epstein-Barr virus, cytomegalovirus, or herpes viruses. Other causes of acute RUQ pain include hepatic infection with abscess formation, which may be of pyogenic, parasitic, or fungal origin [7]. Hepatic tumors may be symptomatic if associated with hemorrhage or rupture. Vascular causes include portal or hepatic vein thrombosis; additional physical exam findings may include hepatomegaly, fever, jaundice, and ascites. Rarely RUQ pain may be caused by peri-hepatic inflammation usually associated with pelvic inflammatory disease [7]. In addition to hepatic causes, right upper quadrant pain may be due to underlying disease of the gallbladder. Biliary colic, which is not colicky but rather a steady and severe ache, usually begins 1–2 h after a meal, usually a fatty meal, lasts 4–6 h, and may be associated with nausea and vomiting. If there is associated fever, persistence of pain, or other symptoms, then the diagnosis is acute cholecystitis, which is a *clinical* diagnosis. Acute cholecystitis is usually caused by gallstones, which may be confirmed via ultrasound. Acute cholangitis caused by bile duct obstruction is also usually caused by stones, although stricture, tumor, parasitic infections, and anatomic abnormalities are other etiologies. Only 70% of patients with acute cholangitis have the classic triage of RUQ pain, fever, and jaundice [5]. Other less common causes include acalculous cholecystitis, biliary sludge, and primary gallbladder or biliary cancers.

The differential diagnosis of acute right lower quadrant (RLQ) pain is significantly narrower, with appendicitis being the most common cause in both adult and pediatric populations. Anatomic variation of location may alter the classic

clinical presentation of acute appendicitis of periumbilical pain with associated anorexia, nausea, and vomiting followed by migration of the pain to the right lower quadrant, which occurs in about 60% of patients [5, 8]. Laboratory studies may show a leukocytosis, and patients may exhibit fever later in the course; imaging is undertaken when the diagnosis is in doubt, usually via ultrasound or limited CT [AJS]. Other causes of RLQ pain include mesenteric adenitis, pelvic pathology, Meckel's diverticulum, right-sided diverticulitis, or the initial manifestation of inflammatory bowel disease.

Similarly, the differential diagnosis for left upper quadrant (LUQ) pain is limited. Peptic ulcer disease (PUD) and gastritis are the predominant causes, followed by splenic abnormalities including splenic infarct, infection/abscess, thrombosis, or hemorrhage [9]. PUD pain is usually described as gnawing discomfort or a "hunger" pain. Pain of duodenal ulcer (DU) is usually relieved with food, whereas pain of gastric ulcer (GU) is usually worsened by food and, thus, may be associated with nausea and weight loss. Common etiologies of PUD are *H. pylori* and nonsteroidal anti-inflammatory drug (NSAID) use. Diagnosis is clinical, although endoscopy is indicated for refractory or alarm symptoms (e.g., weight loss, bleeding, or early satiety) [5]. Simple splenomegaly may cause LUQ pain, although less likely as an acute cause, unless associated with one of the entities listed above or in the setting of acute sickle cell crisis. Other less common causes of LUQ pain include pathology of the adrenal glands (e.g., hemorrhage, infarct), genitourinary (GU) system (e.g., abscess, pyelonephritis, stones), pleural or diaphragmatic irritation, and complications of pancreatitis (e.g., pseudocyst, hemorrhage). Because the large bowel can overlie all deeper structures, colitis of the proximal left side can also present as LUQ pain [9].

The most common cause of acute left lower quadrant (LLQ) pain is diverticulitis. Acute diverticulitis classically presents with abdominal pain, fever, and leukocytosis, although the latter two may be absent. Although the prevalence increases with age, 33–50% of patients aged <50 years

have diverticula, thus affecting younger patients as well [4]. CT scan with intravenous (IV) contrast is the preferred diagnostic test, although MRI or ultrasound may be substituted in select populations where limiting radiation exposure is desired. Other causes of LLQ pain include urolithiasis, which usually causes flank pain radiating into the groin with associated nausea, vomiting, and hematuria, either gross or microscopic. Diagnosis is straightforward in patients with a history of previous stones; risk factors for first stones include family history, obesity, diabetes, diet, medications, occupations which predispose to dehydration, and underlying medical conditions related to calcium absorption and excretion. Noncontrast CT approaches 100% sensitivity and specificity and is the diagnostic test of choice [4]. Colitis affecting the left colon may present with left lower quadrant abdominal pain and may be of ischemic, infectious, or inflammatory origin. Colitis will usually be associated with fever, diarrhea, either watery or bloody, and leukocytosis. Other less common causes of LLQ abdominal pain include fecal impaction which is more common in the pediatric and geriatric populations.

Diffuse or nonlocalized abdominal pain may be experienced as periumbilical or epigastric. The most common is pain from PUD or gastritis, which usually presents with vague symptoms such as a gnawing discomfort. Etiologies for PUD are as noted above, and smoking and alcohol use are associated with gastritis. Acute pancreatitis is usually experienced as epigastric pain, which radiates to the back in half of patients. Nausea, vomiting, and anorexia are often present, and patients may have an ileus. Causes include gallstones, alcohol abuse, medications, autoimmune disorders, hypercalcemia, and hypertriglyceridemia. In a quarter of cases, no cause of the pancreatitis is identified [5]. In the setting of a supporting clinical picture and a lipase level > 3 times normal, the diagnosis is made; imaging is not necessary for diagnosis although CT scan is often performed [5]. Ultrasound is recommended once the diagnosis is made to evaluate for stones. Other causes of diffuse abdominal pain include intestinal obstruction, which presents with progressive abdominal pain

and distention, nausea, vomiting, and obstipation. Surgical history is key, as adhesions are the most common cause, followed by masses and hernias. Plain abdominal films may identify dilated bowel loops or air/fluid levels, although CT with oral contrast is needed for specific location and cause. Acute mesenteric ischemia, which may be arterial or venous, produces pain out of proportion to the physical exam. The abdominal exam is usually benign early on with peritoneal signs being a late finding. A high index of suspicion is required and affected patients are usually elderly or have vascular risk factors (e.g., thrombotic, ischemic, or hypoperfusion) or vascular disease. Laboratory studies are generally not helpful; CT angiography is the diagnostic test of choice [5]. Hemorrhage, either retroperitoneal, within the rectus sheath, or within retroperitoneal organs such as the kidney, adrenal, or pancreas, may present as diffuse abdominal pain. Hemorrhage may be traumatic or spontaneous, the latter more associated with anticoagulation. Abdominal aortic aneurysm (AAA) may cause abdominal pain as they expand, whereas ruptured AAA may present with severe abdominal pain and hemodynamic collapse. Rupture may occur in the retroperitoneum, causing back or flank pain, and may be misdiagnosed as renal colic, perforation, or ischemia.

Chronic abdominal pain may be constant or intermittent. Most causes of chronic abdominal pain are functional in origin and include functional dyspepsia, constipation-predominant and diarrhea-predominant irritable bowel syndrome (IBS), and functional abdominal pain syndrome. For these entities, visceral hypersensitivity, altered gut motility and microbiota, and psychosocial factors all play a role [10]. Functional dyspepsia is characterized by epigastric burning and pain, early satiety, postprandial fullness, and nausea, usually lasting months, without weight loss or other alarm symptoms and with no pathology found on workup (if performed). Esophagogastroduodenoscopy (EGD) may be required to exclude other diagnoses; *H. pylori* testing should be done. Response to medications known to be effective for functional disorders also aids in confirming the diagnosis.

Symptoms of functional dyspepsia include postprandial (30–60 min) epigastric pain or burning, bloating, nausea, and early satiety without disordered bowel functions. Patients with IBS may also have meal-associated abdominal pain, associated with altered stool consistency or frequency, and pain improved with defecation. The functional abdominal pain syndrome consists of constant or frequently recurring pain, without associated bowel dysfunction, which impairs daily functioning in patients who do not otherwise meet criteria for IBS or functional dyspepsia. Abdominal wall pain, which is primarily musculoskeletal or neurologic, is usually located in the upper abdomen, more frequently right-sided, localized to a 2–3-cm area, and not related to eating or defecation. It is usually related to impingement of a cutaneous nerve as it courses underneath the rectus muscle [6]. Nonfunctional causes of chronic, intermittent abdominal pain are rare, usually systemic, are more severe during acute episodes, and include entities such as familial Mediterranean fever, acute porphyria, hereditary angioedema, endometriosis, and superior mesenteric artery syndrome. Many causes of acute abdominal pain can also cause chronic pain, such as chronic pancreatitis, which may be associated with evidence of exocrine or endocrine insufficiency, chronic PUD/gastritis, chronic mesenteric ischemia, and chronic cholecystitis.

Treatment

Treatment for most causes of acute abdominal pain consists of intravenous (IV) fluid, bowel rest, pain medications, and treatment for nausea and vomiting. IV antibiotic coverage for gram-negative and anaerobic organisms is indicated for acute cholecystitis and acute pancreatitis only if sepsis is suspected. Patients with suspected peritonitis should be referred immediately to emergency services or a surgeon; further discussion of acute peritoneal processes is beyond the scope of this chapter. For bowel obstruction, decompression via nasogastric tube and correction of electrolyte abnormalities are indi-

cated. Early surgical intervention is recommended for acute cholecystitis for improved outcomes, whereas for bowel obstruction about two-thirds to three-quarters of patients may be managed conservatively without surgery [5]. Treatment for PUD is to discontinue any identified offending agent, test and treat for *H. pylori* if positive, and initiate antisecretory therapy. Follow-up EGD is warranted for gastric ulcers only [5]. Current guidelines suggest that uncomplicated diverticulitis may not require antibiotic therapy, whereas complicated cases associated with perforation, abscess formation, free air or fluid, or obstruction require hospitalization and IV antibiotics [4].

Principles of therapy for functional disorders include limited testing and referrals, a supportive and validating physician-patient relationship, consideration of adjunct psychotherapy, dietary and lifestyle modification, judicious trials of medications shown to be effective, and avoidance of opioids. Treatment for functional dyspepsia consists of an initial 6–8-week trial of antisecretory therapy, which should be discontinued if ineffective. Tricyclic antidepressants and promotility agents are next-line therapies [10]. Specific treatment for diarrhea-predominant IBS includes loperamide, anticholinergics, and tricyclic antidepressants, which slow intestinal transit time. Additionally, alosetron, rifaximin, eluxadoline, and clonidine have been approved for treatment of diarrhea-predominant IBS [10]. For constipation-predominant IBS, increased dietary soluble fiber, selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) which increase intestinal transit time, and laxatives are useful. Probiotics may improve bloating and flatus. Treatment for functional abdominal pain syndrome consists of cognitive behavioral therapy (CBT) or other psychological interventions, with behavioral interventions targeted to specific symptoms [10]. Multidisciplinary pain rehabilitation has also been successful [10]. Treatment for abdominal wall pain includes local injection(s) of lidocaine and corticosteroids, neurolysis by phenol injection, or neurec-

tomy [6]. Treatment of other causes of intermittent/chronic abdominal pain is based on etiology.

Clinical Pearls

- The initial assessment of abdominal pain involves an assessment of its severity and timing.
- The differential diagnosis of acute abdominal pain is primarily dictated by the location/quadrant of the pain.
- Physical exam and laboratory findings are useful in helping to focus choice of imaging study.
- A thorough history elucidating the pattern of pain and symptoms is key to making the diagnosis for chronic abdominal pain.

Do Not Miss This!

- Initial evaluation of acute abdominal pain should always include an exam for signs of peritoneal inflammation, which warrants emergent evaluation.
- All patients with a complaint of acute abdominal pain should undergo digital rectal examination with testing for occult blood.
- The evaluation of abdominal pain in women should include a pelvic exam if the differential diagnosis includes ectopic pregnancy, infection, torsion, or other conditions of the female reproductive tract.
- The diagnosis of ischemic bowel requires a high index of suspicion and should always be considered in patients who have risk factors.

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Chapter 33
Abnormal Liver Tests

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Introduction

In general outpatient medical practice, abnormalities of liver tests are often encountered in asymptomatic patients. Different institutions may have different tests in a "liver panel," with the most common panel including assays for albumin, total and direct bilirubin, alkaline phosphatase (AP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Abnormalities in the biochemical tests may suggest various disorders, both intrahepatic and extrahepatic. This section will focus on the tests mentioned above, in addition to tests that measure liver functions in order to provide a basic approach for the evaluation of abnormal findings based on test result patterns.

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Key History and Physical Exam

Normal test result ranges vary by laboratory and are based on the range seen in 95% of healthy individuals in a studied group. By definition, 5% of abnormal test results are actually normal results that lie on the far ends of the normal spectrum [1]. Healthy ALT levels ranged from 29 to 33 IU/L for males and 19–25 IU/L for females when studied in populations without identified risk factors for liver disease. Increasingly, data support a correlation between AST and ALT elevation and mortality [2]. As many patients with abnormal liver tests are asymptomatic, a directed history and physical exam after noting the test abnormalities is necessary to determine which results represent a clinical abnormality requiring further evaluation.

The initial approach to determining the significance of abnormal liver tests is to elicit a thorough patient history. Include a history of systemic diseases, family history of diabetes, autoimmune or liver diseases, and a history of risk factors for liver disease, including alcohol history, current and prior prescription and over-the-counter medications, vitamins, supplements, illicit substance use, new or unknown substance or toxin ingestion or exposure, travel and occupational exposure, and risk factors for viral hepatitis. Risk factors include intravenous drug use, sexual history, tattoos, nonsterile piercings, transfusions, residence in endemic regions, or having parents from highly endemic regions [2, 3].

In most cases, asymptomatic patients will have a normal physical exam. However, signs of a chronic process should be assessed. Examine for fever, scleral icterus or jaundice, skin bronzing, abdominal tenderness, hepatomegaly, and muscle wasting. Signs of chronic liver disease include gynecomastia, spider angiomas, splenomegaly, palmar erythema, caput medusa, a fluid wave and bulging flanks suggestive of ascites, and peripheral edema. Dupuytren's contractures and testicular atrophy may be seen in chronic alcoholic liver disease. Cardiopulmonary and jugular venous examination may suggest heart failure, which can cause hepatopathy.

The next step is to repeat the liver tests; only if there is persistent abnormality or the presence of risk factors should further workup be undertaken.

Decision-Making/Differential Diagnosis

The liver has various functions, including detoxification, excretion, and synthesis of albumin, serum globulins, and coagulation factors. Given the variety of these functions and the variability of sources of abnormalities, the most common liver tests may be normal in the presence of liver disease or abnormal with extrahepatic disease. Developing a complete differential diagnosis for abnormal liver tests requires an understanding of the information each study offers and the additional information further studies beyond the basic panel can provide. Identifying patterns of liver test abnormalities is helpful to establish the differential diagnosis, most commonly a cholestatic disease pattern or a hepatocellular injury pattern.

Liver Studies

Serum albumin is synthesized only in the liver. It has a half-life of approximately 18–20 days; thus, it is a marker for chronic, rather than acute, liver disease [4]. Hypoalbuminemia is a result of decreased synthesis by a damaged liver and is seen most often in cirrhosis. Hypoalbuminemia may also be seen with a normal liver in cases of increased protein loss, as in nephrotic syndrome or protein-losing enteropathies, or with downregulation of synthesis, as with protein malnutrition or certain inflammatory conditions that increase cytokine production [5].

Almost all clotting factors are produced in the liver and have shorter half-lives than albumin. Factor VIII is the only extrahepatically produced clotting factor. Due to their short half-lives, clotting factor measurements are useful as markers

of acute liver biosynthetic function failure. The prothrombin time (PT) and international normalized ratio (INR) are most commonly used as indirect measures of clotting dysfunction as the PT involves multiple clotting factors excluding factor VIII. However, since many of these factors require vitamin K for synthesis, these measures may also be abnormal in altered vitamin K availability states, such as fat malabsorption or obstructive biliary disease. A trial of parenteral vitamin K can help to distinguish normal hepatocyte synthetic function from a state of hepatocellular dysfunction [4].

Aspartate aminotransferase (AST), also known as serum glutamic oxaloacetic transaminase (SGOT), and alanine aminotransferase (ALT), also known as serum glutamic pyruvic transaminase (SGPT), are collectively the serum aminotransferases. The ALT level is more indicative of a liver-specific process as it is predominantly found in the liver, whereas AST is found in large concentrations in cardiac and skeletal muscle as well as a variety of other organs including the kidney and brain [2]. AST and ALT can be released into the blood with hepatocellular membrane injury, although levels do not correlate with the amount of cell necrosis [1]. Given the large variety of normal ranges for transaminases between different laboratories, with no set standard [6], minimal elevations of AST and ALT may not necessarily reflect true clinically significant abnormalities. However, significant elevations, more than two times the upper limit of normal, may reflect a variety of liver conditions.

Alkaline phosphatase (AP) is an enzyme also found in various tissues: the liver, bone, intestine, kidney, and placenta are most common. Within the liver, AP is found in the bile canaliculi, specifically in the membranes of these ductules. Elevation of either the gamma-glutamyl transpeptidase (GGT) level or the 5′-nucleotidase confirms a hepatic origin of the elevated AP. Sending a fractionated AP can also aid in distinguishing the tissue of origin of the elevated AP by separating out the alkaline phosphatase isoenzymes from each distinct tissue that make up the total serum AP. An elevated AP of hepatic origin may be present with either a normal or

elevated bilirubin; this association will help to establish a differential diagnosis.

Serum bilirubin levels may be a marker of the excretory function of the liver. Bilirubin is a product of the catabolism of heme proteins, predominantly hemoglobin. Unconjugated bilirubin is insoluble in water; once it is bound to albumin (i.e., "conjugated") by the liver, it becomes hydrophilic and can be excreted in bile and urine. The indirect fraction of bilirubin measures unconjugated bilirubin, whereas conjugated bilirubin makes up the direct fraction. Again the pattern of elevation of each fraction of bilirubin is useful to elucidate etiology [5].

Establishing Patterns of Abnormalities

The two main patterns of abnormalities encountered are of hepatocellular injury, usually with an elevation of the serum transaminases, and of cholestatic disease, with predominant AP elevation with or without hyperbilirubinemia. These patterns are important in determining the type of disease and the subsequent diagnostic evaluation and management. Isolated hyperbilirubinemia without AST, ALT, or AP elevation may also be seen. Beyond assessing the category of liver injury in suspected liver disease, it is also important to determine the level of liver function using the albumin and INR as mentioned previously. See Fig. 33.1 for an algorithm of diagnostic evaluation of abnormal liver tests.

A predominantly elevated AST and ALT pattern indicates hepatocellular injury. The serum bilirubin and alkaline phosphatase may also be elevated, but less prominently than the aminotransferases. Although ALT is more specific for the liver, both AST and ALT are sensitive for liver cell injury. A normal creatine phosphokinase (CPK) level points away from muscle as the source of elevation in aminotransferase levels, whereas if the CPK and aldolase levels are elevated, muscle disease as the source of elevated AST and ALT is more likely. (A discussion of muscle conditions is outside the

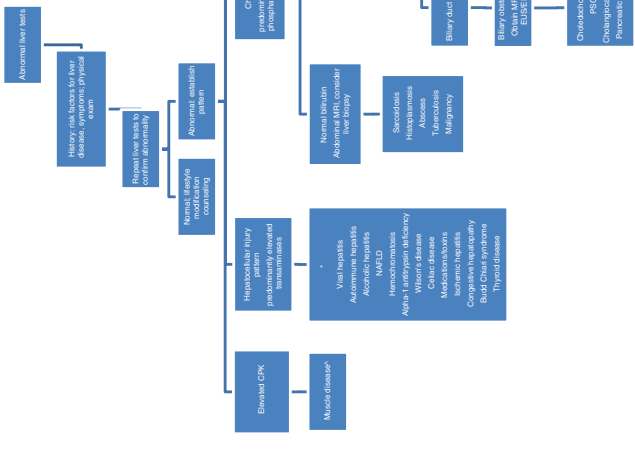

FIGURE 33.1 Abnormal liver test evaluation. ^Muscle disease outside the scope of this chapter. *See Table 33.1

scope of this chapter.) The magnitude of transaminase elevations can also aid in the differential diagnosis by degree and pattern of AST to ALT elevation. Severe elevations of AST and ALT to over 1000 units/L are most commonly seen in ischemic hepatitis, toxin–/drug-induced injury, acute viral hepatitis, and acute Budd–Chiari syndrome (occlusion of the hepatic veins). Obtaining a medical, drug, and toxin history, vascular imaging with Doppler ultrasound, and viral serologies for hepatitis A (HAV), hepatitis B (HBV), and hepatitis C (HCV) are warranted, and further testing for Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV) can be considered, especially in immunocompromised patients. While a large number of medications have been reported to cause liver injury, a list of the more common toxins and drugs are listed in Table 33.1 [1, 4, 7–9]. Common causes of milder elevations

Table 33.1 Common agents that cause elevations in liver enzyme levels

Medications	Acarbose, acetaminophen, allopurinol, amiodarone, aspirin, baclofen, bupropion, calcium channel blockers, carbamazepine, ciprofloxacin, didanosine, fluconazole, glipizide, glucocorticoids, HMG-CoA reductase inhibitors, isoniazid, ketoconazole, methotrexate, nitrofurantoin, nonsteroidal anti-inflammatory drugs, phenytoin, pyrazinamide, rifampin, risperidone, selective serotonin reuptake inhibitors, synthetic estrogens, synthetic penicillins, tamoxifen, tetracycline, trazodone, valproic acid, zidovudine
Drugs of abuse	Anabolic steroids, cocaine, MMDA, methamphetamine, phencyclidine, toluene-containing glues/solvents
Herbs and complimentary/ alternative therapies	Alchemilla, chaparral, Chinese herbs (jin bu. huan, ephedra), germander, gentian, kava kava, scutellaria, senna, shark cartilage

of the AST and ALT include nonalcoholic fatty liver disease (NAFLD), chronic viral hepatitis due to HBV or HCV, alcoholic liver disease, and autoimmune hepatitis (AIH). NAFLD is increasing in developed countries mirroring increasing rates of obesity, with studies showing prevalence from 57.5% to 74% in obese patients, and cannot be diagnosed with serologic testing alone. It can be detected as increased echogenicity on abdominal ultrasound although elastography or liver biopsy is needed to confirm the diagnosis and to establish the presence and degree of inflammation and fibrosis [7, 10]. These histologic features indicate nonalcoholic steatohepatitis (NASH), which carries the potential for progression to cirrhosis [2]. Serologies for AIH include an antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), and anti-liver–kidney microsomal antibody (ALKM-1 Ab). Less common hepatic causes of mild, but chronically, abnormal aminotransferases are Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency. Nonhepatic causes of milder AST and ALT elevations include celiac disease, thyroid disease, and congestive hepatopathy from congestive heart failure. An anti-tissue transglutaminase antibody can direct the diagnosis toward celiac disease in a patient with symptoms of intestinal bloating and diarrhea, as about 40% of patients have abnormal liver tests when diagnosed with celiac sprue [11]. A serum thyroid-stimulating hormone assesses for thyroid abnormalities, and a transthoracic echocardiogram may be obtained to evaluate for heart failure. See Table 33.2 for further diagnostic workup of hepatocellular injury by etiology.

Beyond the level of elevation, the ratio of aminotransferases is also relevant for diagnosis. Most acute liver processes produce an AST/ALT ratio < 1; this can be found in nonalcoholic fatty liver disease and chronic viral hepatitis, but as the injury progresses to cirrhosis, the ratio changes to >1. An AST/ALT ratio > 2:1 is suggestive of alcohol as the cause of liver injury [1].

Cirrhosis is the product of a slow transformation of the injured liver into a scarred or fibrotic nodular organ with

Table 33.2 Diagnostic evaluation of hepatocellular injury

Viral hepatitis	HAV IgM, HbsAg, HBcAb, HCV Ab; consider CMV, EBV, HSV, VZV
Autoimmune hepatitis	ALKM-1 Ab, ANA, ASMA
Alcoholic hepatitis	History, AST:ALT ratio > 2–3:1
NAFLD	HbA1c, lipid profile, medication review, abdominal ultrasound; consider liver biopsy
Hemochromatosis	Iron studies (including transferrin saturation, ferritin); consider HFE gene testing if positive
Alpha-1 antitrypsin deficiency	Serum AAT level
Wilson's disease	Ceruloplasmin level
Celiac disease	Anti-tissue transglutaminase antibody
Medications/toxins	Review and discontinue hepatotoxic medications
Ischemic hepatitis	Assess causes of hypoperfusion
Congestive hepatopathy	Assess heart failure
Budd–Chiari syndrome	Obtain vascular imaging with Doppler US of abdomen
Hypo- or hyperthyroidism	TSH

reduced function. It is important to note that as hepatocellular injury progresses to cirrhosis, normalization of the AST and ALT is often seen. However, the various functions of the liver may be affected; it then becomes important to assess the level of biosynthetic or excretory functions of the liver, as both can be significantly reduced in cirrhosis.

In contrast to a hepatocellular injury pattern, a modest to severe elevation of alkaline phosphatase is the hallmark of

cholestatic disease. As mentioned previously, it is not exclusive to the liver and can be narrowed to being of hepatic origin using 5′-nucleotidase or GGT or by fractionating the AP. The serum bilirubin may often also be elevated, both the total and direct fractions; however, it may also be normal. With an elevated serum bilirubin, the next step is to obtain an abdominal ultrasound. Biliary ductal dilation suggests biliary obstruction due to choledocholithiasis, cholangiocarcinoma, pancreatic cancer, or primary sclerosing cholangitis (PSC). Endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) may be used to confirm the obstruction. Endoscopic retrograde cholangiopancreatography (ERCP) can both visualize the obstruction and obtain tissue biopsy. Elevated AP and elevated bilirubin in the absence of bile duct dilation may be due to primary biliary cirrhosis (PBC), sepsis, or a medication effect: a positive anti-mitochondrial antibody (AMA) points to PBC as the diagnosis [4].

An elevated AP with normal bilirubin is most suggestive of infiltrative diseases. These may include sarcoidosis, histoplasmosis, tuberculosis, or malignancy, either primary hepatocellular carcinoma (HCC) or metastatic disease. Infectious hepatic abscesses may also follow this pattern. An abdominal magnetic resonance image (MRI) and liver biopsy may be indicated to evaluate for these disorders [4]. The level of AP is normally elevated during pregnancy, as it is produced by the placenta.

Isolated indirect bilirubinemia is most often due to hemolysis or hematoma reabsorption, Gilbert's syndrome, or less commonly Crigler–Najjar syndrome [3]. These latter two are hereditary defects of conjugation. Isolated direct bilirubinemia is usually secondary to Dubin–Johnson syndrome or Rotor's syndrome, which are inherited defects in hepatic excretion of bilirubin. Conjugated hyperbilirubinemia may also be seen in pregnancy, so a pregnancy test should be performed in women of childbearing age.

Treatment

Risk factor reduction, including substance use, and weight reduction counseling and discontinuation of hepatotoxic substances or medications are important therapeutic measures to undertake in the general medical office and can improve liver injury related to inflammation and prevent mortality from liver disease [12]. Management of diabetes and hyperlipidemia are indicated as well for NAFLD. Chronic hepatitis C infection is increasingly being managed and treated by primary care physicians. Often, very mild test abnormalities (less than three times the upper limit of normal of the aminotransferases) that are caused by medication therapy, such as statins, can be monitored in the primary care setting, especially when continuing the medication. A modest or severe elevation of aminotransferases should prompt discontinuation of hepatotoxic medications. With severe abnormalities and acute liver dysfunction associated with an elevated INR and often hyperbilirubinemia or encephalopathy, patients require hospital admission to identify the cause, to initiate supportive management, or to monitor the need for transplantation [2]. Gilbert's syndrome is often noted in the primary care setting; it is benign. Further specialty care referral is recommended for management of other genetic disorders of bilirubin metabolism, hereditary disorders such as hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, and also autoimmune hepatitis.

Clinical Pearls

- Not all institutions have similar liver tests in a liver panel, reference ranges vary, and 5% of abnormal tests are at the ends of the spectrum of the normal range.
- The liver's biosynthetic function is not directly measured using AST and ALT; the albumin level is a measure of chronic liver function; clotting factors are a measure of acute liver function.

- A thorough history of risk factors for liver disease helps to direct initial diagnostic evaluation and further laboratory testing.
- Identifying the pattern of liver test abnormalities helps to establish a differential diagnosis.

Do Not Miss This!

- Interpretation of liver tests requires detailed knowledge of the institution-specific normal ranges, variability in assays, and chronicity of abnormalities.
- Acute toxin exposure may require hospitalization for supportive care and possibly transplantation.

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Part XI
Psychiatric

Chapter 34
Depression/Anxiety

Daniel Pomerantz and Ashutosshh Naaraayan

Introduction

Depression is the most common psychiatric disease worldwide in the general population with the lifetime risk being 13.23% (95% confidence interval, 12.64–13.81) [1]. It is almost twice as common in women as compared to men and more common in developed countries than the developing world [1, 2]. Depression is underrecognized in the primary care setting as it presents with somatic symptoms (headache, back pain, chronic pain, etc.) in up to two-thirds of the affected patients [3]. Patients are not forthcoming about depressive symptoms unless asked directly, for various reasons including, but not limited to, fear of stigmatization, considering such symptoms to be their personal flaw rather than an illness, misconception that depressive symptoms can only be assessed by a psychiatrist, and concerns about being prescribed an antidepressant medication [4]. The comorbid state of depression with other chronic diseases incrementally worsens health when compared with depression alone, with any of

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the chronic diseases alone, and with any combination of chronic diseases without depression [5]. Patients with depression have an increased risk of mortality (1.81 [95% CI: 1.58–2.07]) [6].

Generalized anxiety disorder (GAD) is characterized by excessive and persistent worrying about everyday things and situations that is hard to control, causes significant distress or impairment, and occurs on more days than not for at least 6 months [7]. In the United States, the lifetime prevalence of GAD is about 5.1% [1]. The disorder is approximately twice as common in women as it is in men [1].

GAD frequently occurs in conjunction with either major depression or other anxiety disorders [8]. Patients with comorbid major depression and GAD tend to have a more severe and prolonged course of illness and greater functional impairment. The presence of comorbid major depressive episodes is associated with a poorer prognosis in patients with GAD [9].

Key History and Physical Exam and Differential Diagnoses

Depression may refer to a depressed state of mood in everyday language. A syndromic definition of depression looks to identify a set of specific symptoms to define a depressive disorder. The syndrome of major depressive disorder (MDD) as illustrated in Fig. 34.1 could be a consequence of one of the various disease states such as unipolar major depression, bipolar disorder, schizophrenia, substance−/medication-induced depressive disorder, and depressive disorder due to another (general) medical condition [7].

Once the symptoms for depression (as listed in Fig. 34.1) have been evaluated, an assessment of the severity of impact on social, interpersonal, and occupational functionality should be carried out. In addition, clinicians should assess the duration of symptoms and inquire about previous manic or hypomanic symptoms/episodes. Patients should be asked

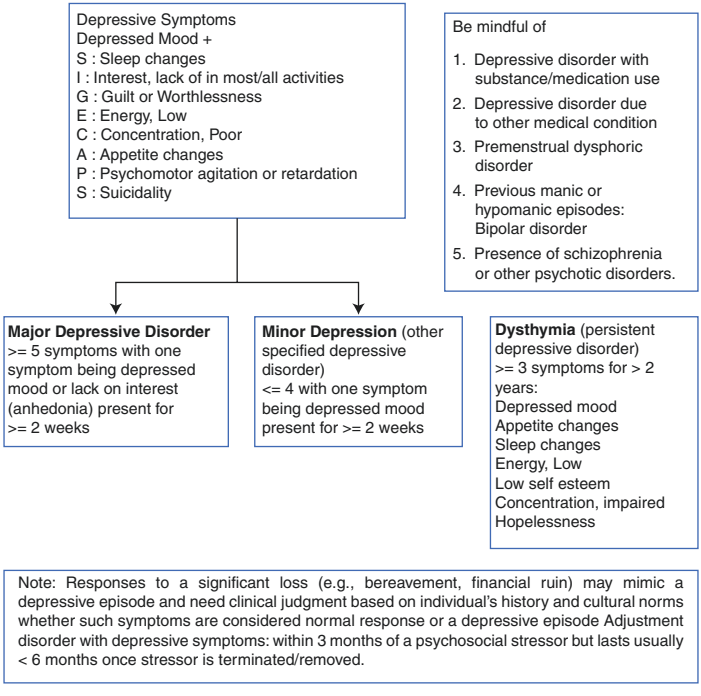

FIGURE 34.1 Evaluation for syndrome of major depressive disorder

directly and specifically about any current or past suicidal ideation or thoughts. Patients reporting suicidal thoughts should be asked about specific plans, especially about access to firearms. Recent efforts in New Hampshire and elsewhere to promote temporary transfer of firearms out of the household of a suicidal person seem to be effective at preventing gun suicides [10]. Extreme risk protection orders (ERPO) which allow firearms to be removed from a person who is at risk of harming himself/herself or others seem to prevent suicides. One study estimated that for every 10 gun removals, one suicide was prevented [11]. General medical illnesses are present in ~70% of patients with MDD. Cardiovascular (hypertension), musculoskeletal (arthritis), and respiratory diseases (COPD) are more commonly associated with MDD

although every organ system has been known to coexist with MDD [9]. The relationship between medical comorbidities and depression is bidirectional as is seen in case of obesity. Patients with depression tend to be at an increased risk of becoming obese (odds ratio 1.6), and obese patients are at increased risk of being depressed (odds ratio 1.6) [12].

Although excessive and persistent worrying is the pathognomonic feature of GAD, the most common presenting symptoms are hyperarousal (poor sleep, fatigue, difficulty relaxing), autonomic hyperreactivity, and muscle tension (headache, neck, shoulder, and back pains). Although the worry is clearly excessive, the concerns involve the same areas of life (family and interpersonal relationships, work and finances, and health) as in non-anxious adults [13]. GAD typically has a gradual onset with subsyndromal anxiety common before the age of 20 years and eventual progression of anxiety in later years [14]. Because of the association of GAD with increased baseline heart rate, decreased heart rate variability, and hypertension, there is a growing literature suggesting the association of GAD with the development of coronary heart disease [15].

Patients with comorbid major depression and GAD tend to have a more severe and prolonged course of illness and greater functional impairment [16].

Treatment

The generalized anxiety disorder seven-item (GAD-7) scale can be used to screen for GAD in primary care, and it can also be used to monitor treatment response [17]. The Hospital Anxiety and Depression Scale (HADS) has the benefit of assessing and monitoring the severity of symptoms of both anxiety and depression [18]. An algorithm suggested for screening and treatment for GAD is presented in Fig. 34.2.

The US Preventive Services Task Force recommends screening all adults (age > 18 years) for depression at least once and using clinical judgment to determine whether to do additional screening for high-risk patients [19]. The PHQ-2 is

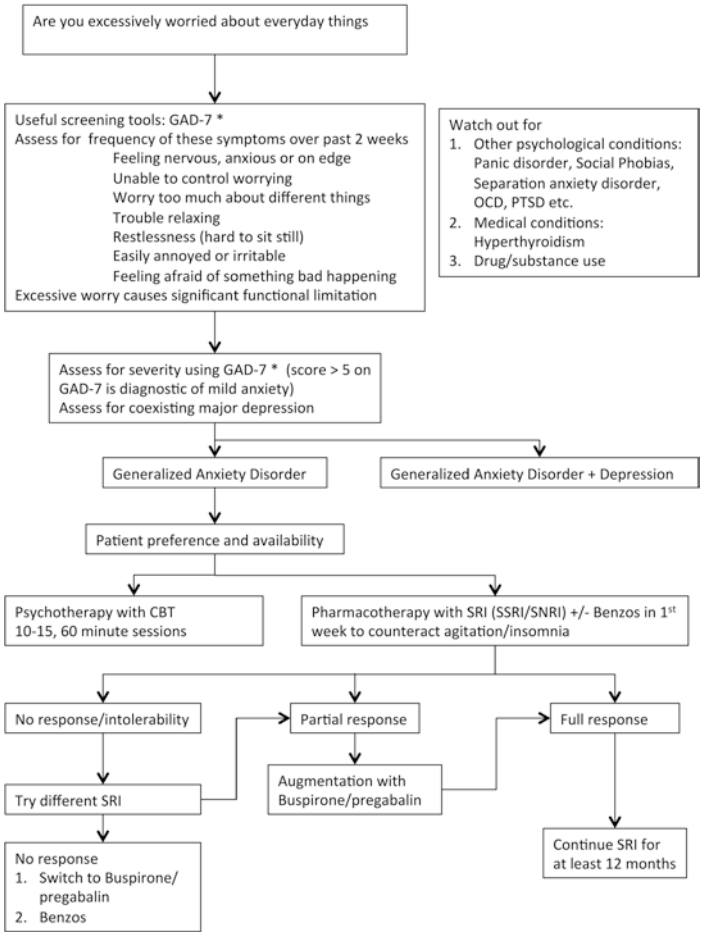

FIGURE 34.2 Suggested algorithm for screening and management of generalized anxiety disorder. Reprinted with permission [17]

a very brief, two-question instrument, which offers acceptable properties as screening tool; it should not, however, be considered adequate for diagnosis [20]. An algorithm for screening and treatment recommendations for major depressive disorder is shown in Fig. 34.3.

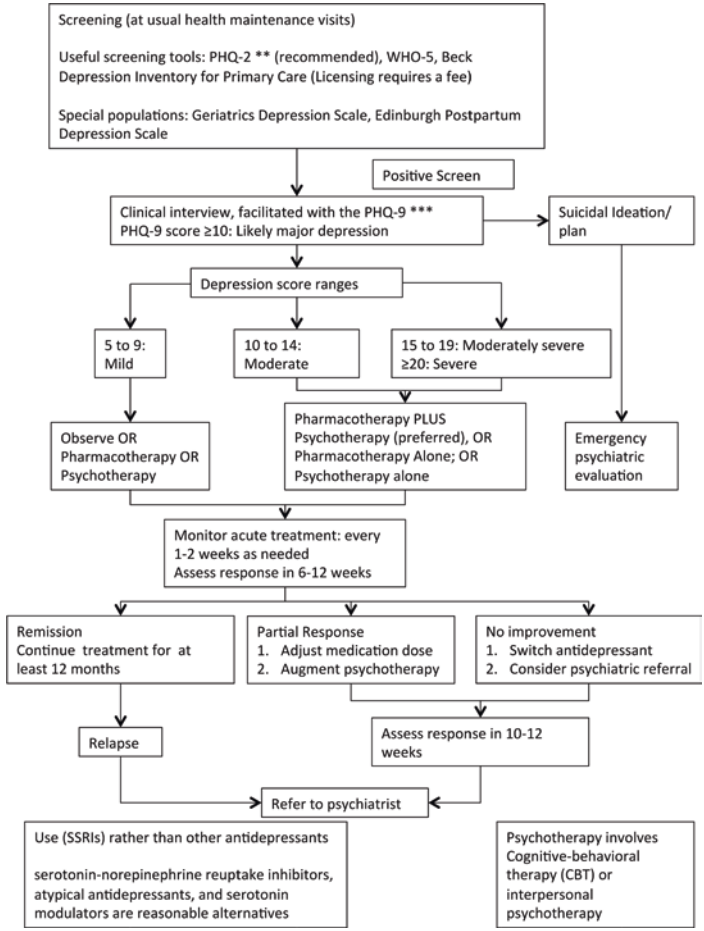

FIGURE 34.3 Suggested algorithm for screening and management of major depressive disorder. Reprinted with permission [21, 22]

A list of medications commonly prescribed for MDD, with their usual daily dosages and side effect profiles, is listed in Table 34.1 [23].

Primary GAD with secondary depressive symptoms can be difficult to distinguish from major depressive disorder or

Table 34.1 Commonly prescribed medications for major depressive disorder and their adverse effects

Name	Usual daily dose (mg/day)	Adverse effects
Selective serotonin reuptake inhibitors (SSRI)		
Escitalopram	10–20	Insomnia, orthostasis, QTc prolongation, GI disturbances, sexual dysfunction, weight gain
Fluoxetine	20–60	
Sertraline	50–200	
Serotonin-norepinephrine reuptake inhibitors (SNRI)		
Duloxetine	60–120	Insomnia, GI disturbances
Venlafaxine	75–375	Drowsiness, insomnia, QTc prolongation, GI disturbances, sexual dysfunction
Atypical antidepressants		
Bupropion	300	Insomnia, agitation, QTc prolongation, GI disturbances
Mirtazapine	15–45	Anticholinergic, drowsiness, QTc prolongation, weight gain, mild sexual dysfunction
Tricyclic antidepressants (TCA)		
Imipramine	150–350	Anticholinergic, drowsiness, orthostasis, QTc prolongation, GI disturbances, weight gain, sexual dysfunction
Monoamine oxidase inhibitors (MAO inhibitors)		
Selegiline	6–12 mg/24-h patch	Anticholinergic, insomnia, orthostasis

persistent depressive disorder (dysthymia), as the conditions share many features such as an insidious onset, protracted course, prominent dysphoria, and anxiety symptoms. Broadly, individuals with depression tend to brood self-critically on previous events and circumstances, whereas patients with

GAD tend to worry about possible future events. Symptoms of depression such as early morning awakening, diurnal variation in mood, and suicidal thoughts are all uncommon in GAD.

Clinical Challenges

Since patients may be reluctant to accept a diagnosis of anxiety or depression, it may be necessary to negotiate a way forward. Avoid focusing on disagreements about the diagnosis, but rather try to find ways to agree on treatment for the symptoms which are troubling to the patient [24]. In addressing these sometimes emotional subjects with patients, use empathy—the ability to understand the patient's situation, perspective, and feelings and to communicate that understanding to the patient [25]. Demonstrate empathy by using techniques like "active listening" to identify the patient's emotions, and assess the intensity of their feelings. Avoid offering false reassurances; sometimes the most important thing to a patient is the doctor's presence with them in the struggle [22].

Clinical Pearls

Depressed people may be more mindful of pain than nondepressed people. Treat depression first if the source or severity of pain is uncertain and clinical assessment unrevealing.

Sleep problems and appetite changes are common in the elderly, so consider depression when hearing about these symptoms.

Do Not Miss This!

Grieving and depression are similar early on. A patient with prolonged grieving should be evaluated for depression.

Hypothyroidism can masquerade as depression, especially in the elderly.

Always evaluate medications and drugs in a patient with depression.

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Chapter 35
Insomnia

Aaron D. Storms and Shadi Dowlatshahi

Introduction

Insomnia is one of the most common patient complaints in the ambulatory setting. It is defined as difficulty with initiating sleep, maintaining sleep, or waking up too early despite adequate opportunity and circumstances for sleep, which results in some form of daytime impairment [1]. The prevalence of insomnia varies based on the criteria used to define insomnia; however, an estimated 35–50% of adults present symptoms of insomnia, with about 5–15% having chronic insomnia [2, 3]. The prevalence is higher in older adults [4]. Risk factors for insomnia include female sex, increased age,

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low socioeconomic status, unemployment, homelessness, being a veteran, and the marital status of divorced, widowed, or separated [3, 5–7]. Patients with comorbid medical or psychiatric conditions are at even higher risk [5, 8, 9].

Insomnia is classified as short-term when it has a duration of <3 months and chronic when ≥3 months [1]. Short-term insomnia is typically precipitated by stressful life changes such as personal loss and changes in sleep environment and may recur when new or similar stresses present. Once the patient adapts to the new stressor or it resolves, the insomnia is expected to resolve as well. However, for some patients it becomes a chronic problem [1].

Although chronic insomnia may be associated with several medical and psychiatric conditions, the third edition of the International Classification of Sleep Disorders (ICSD-3) moved away from subclassifying chronic insomnia as primary and secondary (comorbid). One concern with the old classification was that the management of patients diagnosed with "secondary" insomnia focused on treating the underlying condition without adequate management of the sleep disorder. Another consideration was that patients with chronic insomnia, regardless of associated comorbidities, usually develop cognitive processes and behaviors that perpetuate the condition, which must be addressed in a targeted way [1, 10].

Patients with chronic insomnia are at higher risk for health consequences, in addition to reporting a poorer quality of life and impaired occupational and social life. They have higher rates of healthcare utilization including hospitalizations, primary care visits, medication use, and higher healthcare costs [11, 12]. Insomnia is associated with losses of quality-adjusted life-years [13], and some work-related impacts include lost productivity, lower work performance, higher rates of absenteeism, and increased errors [12, 14]. Thus, it is important to identify and treat insomnia in a timely manner.

Key History and Physical Exam

A detailed history and physical exam should be performed at the time of presentation. It is important to assess for a potential association to medical or psychiatric conditions, medication effect, substance use history, and recent stressors.

History

Patients should be asked about their sleep history to determine the type of symptoms (i.e., issues with sleep initiation, maintenance, or early awakening), the duration (i.e., short-term or chronic), the frequency, and the course (i.e., recurrent or persistent). Questions regarding alleviating versus provoking factors, sleep schedule, activities prior to bedtime, and daytime dysfunction should also be solicited. Examples of questions to ask patients may include [3, 15, 16]:

- How long has this problem been occurring? How often does it happen?
- Do you have problems falling asleep? How long does it take you to fall asleep?
- Do you have problems staying asleep? How often do you wake up at night and for how long?
- Do you wake up too early in the morning? What time do you usually wake up?
- How is this impacting the way you feel and function during the day?

Assess sleep hygiene:

- What time do you go to bed every night and get out of bed every morning? (weekdays versus weekends).
- How long do you typically sleep?
- What kind of work hours do you have? Are you a shift worker?

- Describe your sleeping environment in regards to noise, temperature, light, etc.
- Describe your activities before bedtime. How do you unwind?
- Do you watch TV or read in bed prior to going to sleep?
- Do you take daytime naps?
- What do you do if you cannot fall asleep?

Patients should be asked about daytime consequences of poor sleep. Common symptoms they may experience include fatigue, decreased energy, lack of concentration, mood disturbances, and concern about sleep [1]. The Epworth Sleepiness Scale questionnaire may be administered to better assess patient complains of excess daytime sleepiness, as these may indicate a different sleep disorder from insomnia [3, 17]. These patients should also be evaluated for safety and advised to avoid driving or operating heavy machinery when they are drowsy.

All patients should maintain a sleep diary for about 2 weeks. It should include their bedtime, time until sleep onset, length of sleep, number and duration of awakenings, quality of sleep, wake-up time, time getting out of bed, use of sleep aids, nap times, and daytime symptoms [3, 15, 18]. The diary may later be used as a baseline for comparison when treatment is initiated. If patients have a sleeping partner, they should be asked about patient behaviors (e.g., snoring, limb movements, episodes of apnea).

Social History

Patient's alcohol, caffeine, tobacco, and drug history should be evaluated. One should inquire about occupation and work/school hours and determine if the patient is a shift worker. Recent stressors should be assessed (e.g., new job, change in location, change in relationship, financial or social stressors), especially in cases of short-term insomnia.

Medical History

A thorough review of systems and medical history should be obtained to reveal any psychiatric or medical conditions that may be present. Specifically, patients should be evaluated for mood and anxiety disorders which account for a large proportion of psychiatric disorders associated with chronic insomnia [3, 16]. Patients with posttraumatic stress disorder also frequently report insomnia [19].

Common medical comorbidities associated with insomnia include pulmonary disease, neurologic disease, heart disease, hypertension, diabetes, malignancy, gastrointestinal conditions, and chronic pain [5, 8, 9, 18]. Evaluation for sleep apnea, covered in another chapter, should be considered in patients with obesity and a history of snoring.

Medication History

Medications that can contribute to insomnia include [3, 5, 9, 18]:

- Central nervous system stimulants (i.e., caffeine, methylphenidate, amphetamine, modafinil).
- Respiratory stimulants (i.e., theophylline, albuterol).
- Cardiovascular agents (i.e., beta blockers, diuretics, alpha agonists and antagonists, calcium channel blockers).
- Antidepressants (i.e., selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, norepinephrine and dopamine reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors).
- Allergy medications (i.e., pseudoephedrine, phenylephrine).
- Hormones (i.e., glucocorticoids, thyroid medication).

Withdrawal of sedatives, hypnotics, opioids, or glucocorticoids may precipitate insomnia.

Physical Exam

There is no specific physical exam finding consistent with diagnosing insomnia; however, the physical exam may reveal findings consistent with an underlying medical condition (e.g., high blood pressure). Certain exam features that should be specifically addressed include obesity, neck circumference, and upper airway obstruction to diagnose sleep apnea [3, 18].

Differential Diagnosis

Diagnoses to consider in the differential for insomnia include [1, 3, 18]:

- Medication-induced insomnia.
- Sleep-related breathing disorders (e.g., obstructive sleep apnea, Cheyne-Stokes breathing).
- Short-duration sleep (normal short sleepers).
- Chronic volitional sleep restriction (insufficient sleep syndrome).
- Sleep-related movement disorders (e.g., restless leg syndrome, periodic limb movement disorder).
- Circadian rhythm sleep-wake disorders.
- Sleep-disruptive environmental circumstances.

Decision-Making

Insomnia is a clinical diagnosis and is based on sleep history. Diagnosis of insomnia includes meeting the following criteria per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Sleep Disorders, Third Edition (ICSD-3) [1, 20]:

- Difficulty in initiating sleep, maintaining sleep, or early-morning awakenings.

- Occurs despite ample opportunity for sleep.
- Daytime impairment in function due to sleep difficulty.
- The sleep difficulty is not better explained by another sleep disorder.
- For chronic insomnia, the symptoms occur at least 3 days per week, for at least 3 months.

No specific workup is needed to diagnose insomnia. As mentioned above, patients should maintain a sleep journal for 2 weeks in order to aid in the diagnosis, and it may be used during treatment to evaluate progress.

Polysomnography is not routinely indicated, but patients may benefit from this test if there is concern for sleep apnea or for patients with suspected restless leg syndrome/periodic limb movement disorder [1, 3]. Actigraphy is another test modality that may help in documenting patients' sleep patterns and circadian rhythms. It is measured at home and it works by monitoring a patient's movement. Actigraphy may be useful when there is concern for the reliability of the clinical history or the sleep journal or when there is suspicion for a circadian rhythm disorder [3, 21]. Other tests that may be beneficial include psychiatric screening tools to assess for depression and anxiety. There are no routine laboratory or imaging tests that should be obtained, unless a medical comorbidity is suspected (e.g., echocardiogram, thyroid function tests, hemoglobin A1c, iron studies).

Treatment

The goal of treatment is to improve sleep quality and daytime functioning [18, 22]. Comorbid conditions, including medical, psychiatric, and substance abuse, should all be addressed and treated, as they may be contributing to the symptoms of insomnia. See Fig. 35.1.

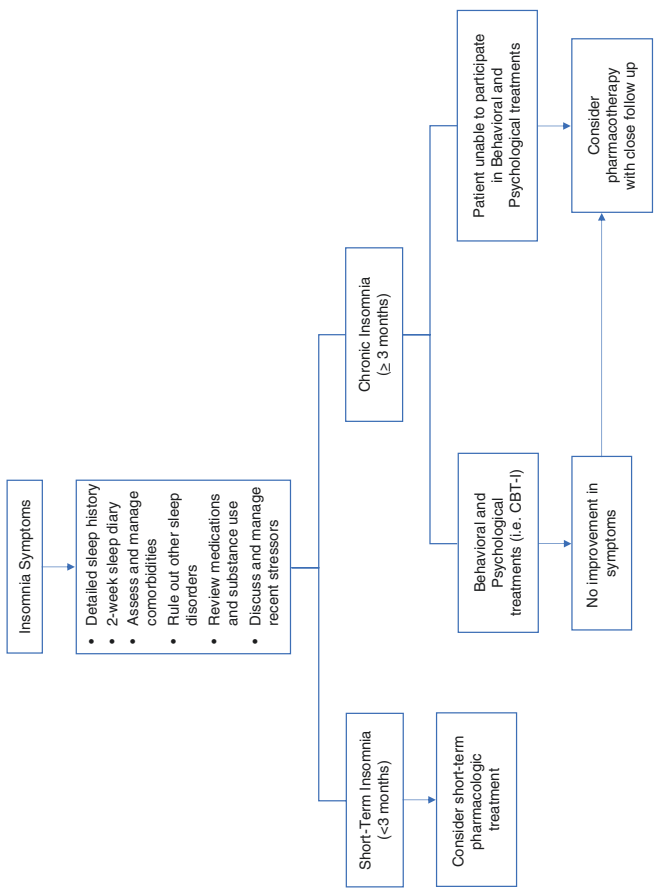

FIGURE 35.1 Insomnia algorithm

Behavioral and Psychological Therapies

The American Academy of Sleep Medicine (AASM) and American College of Physicians both endorse the use of behavioral and psychological therapies, specifically cognitive behavioral therapy for insomnia (CBT-I), as first-line treatment in chronic insomnia [2, 22, 23]. However, AASM acknowledges that not all patients with chronic insomnia are able to receive behavioral treatments or benefit from them; therefore, pharmacotherapy should continue to be considered as adjunct or stand-alone treatment [24].

Cognitive Behavioral Therapy for Insomnia (CBT- I)

Multicomponent CBT-I involves combining several of the therapies mentioned below (stimulus control, sleep restriction therapy, education about sleep hygiene, relaxation strategies, among others) along with cognitive strategies that help patients recognize and change unhelpful beliefs and anxieties about sleep. It is typically delivered by trained professionals over 4–8 weeks. The AASM strongly recommends CBT-I, explaining that almost all patients should receive it given evidence for important clinical improvements. The effects of CBT-I seem to be sustained long-term, and the need for medications may be reduced. The limitations include a lack of clinicians trained to deliver the therapy and the amount of time required [2, 18, 23, 25, 26].

Multicomponent Brief Therapies

Similar to CBT-I, these brief therapies are multicomponent and draw from several of the therapies listed below. However, unlike CBT-I, brief therapies typically only last 1–4 weeks. The body of evidence is not as robust as for CBT-I, but sufficient for AASM to suggest that patients receive this therapy [2, 23].

Stimulus Control

Patients undergoing stimulus control therapy are provided with strategies to associate their bed with sleeping time, as opposed to arousal time. For example, they are instructed to use the bed only for sleeping and sexual activity, only getting in bed or staying in bed if sleepy, and waking up at the same time every day. AASM supports using stimulus control as an element in multicomponent therapies or as a single therapy [2, 18, 23].

Sleep Restriction Therapy

Patients with insomnia may be prone to spend more time in bed to compensate for lack of sleep, which may further perpetuate the problem. Sleep restriction therapy entails limiting the time the patient spends in bed, in order to increase the sleep drive. The patient is instructed to spend the same amount of time in bed as they do sleeping, but no less than 5 h. The time interval increases or decreases every week, based on the patient reports of sleep efficiency (sleep efficiency = time asleep/time in bed). AASM supports using sleep restriction as an element in multicomponent therapies or as a single therapy [2, 18, 23].

Relaxation Therapy

Patients are taught techniques to help reduce arousal prior to bedtime or during nighttime awakenings. These include abdominal breathing, tension and relaxation of muscle groups, guided imagery, and meditation. AASM supports using relaxation as an element in multicomponent therapies or as a single therapy [2, 18, 23].

Sleep Hygiene

Sleep hygiene should be part of a multicomponent approach; however, AASM has recommended *against* using sleep hygiene as a single therapy for chronic insomnia due to data showing low benefits. It includes rectifying behaviors that are incompatible with sleep such as avoiding caffeine, alcohol, and nicotine before bedtime. It also involves lifestyle changes (e.g., diet, exercise) and correcting nighttime environmental factors (e.g., noise, lighting, temperature) [2, 18, 23].

Other Behavioral and Psychological Therapies

Several other therapies are available, including cognitive, biofeedback, paradoxical intention, intensive sleep retraining, and mindfulness therapies. However, AASM did not identify enough evidence to provide a recommendation in favor or against them in their latest guideline [2, 23].

Medications

Pharmacotherapy may be considered in patients with chronic insomnia who do not have access or cannot participate in behavioral and psychological treatments for chronic insomnia and in patients who do not improve despite such treatments [24]. Patients with short-term insomnia may also benefit from pharmacological treatment. The decision to start pharmacotherapy should be individualized and a shared decision-making approach should be used [22]. FDA-approved medications that are currently recommended by the AASM for the treatment of insomnia include benzodiazepines, "Z-drugs" (nonbenzodiazepine receptor agonists), ramelteon, doxepin, and suvorexant [24] (Table 35.1).

Table 35.1 FDA-approved medications clinically recommended by AASM for the treatment of insomnia

Drug name	Classification	Dosage (mg)	Indication	Most common side effects [27]
Temazepam	Benzodiazepine	7.5–30	Sleep onset and maintenance	Drowsiness, headache, fatigue, nervousness, lethargy, dizziness
Triazolam	Benzodiazepine	0.125–0.5	Sleep onset	Drowsiness, dizziness, lightheadedness, coordination disorder/ataxia
Eszopiclone	Z-drug	1–3	Sleep onset or sleep maintenance	Headache, unpleasant taste, somnolence, dry mouth, nausea, dizziness, nervousness, respiratory infection, dyspepsia, depression
Zaleplon	Z-drug	5–20	Sleep onset	Headache, dizziness, abdominal pain, nausea, somnolence, asthenia, eye pain, dysmenorrhea

Zolpidem	Z-drug	5–10	Sleep onset	Headache, drowsiness, dizziness, sinusitis
Zolpidem controlled release	Z-drug	6.25–12.5	Sleep onset or sleep maintenance	
Ramelteon	Melatonin agonist	8	Sleep onset	Dizziness
Suvorexant	Orexin receptor agonist	10–20	Sleep maintenance	Headache, somnolence
Doxepin	Tricyclic antidepressant	3–6	Sleep maintenance	Somnolence/sedation, upper respiratory tract infection

The selection of a pharmacological agent must consider several factors, including characteristics of insomnia (i.e., sleep onset versus sleep maintenance), prior treatment responses, comorbid conditions, patient preference, patient-specific concerns for adverse outcomes, characteristics of the medication such as duration of effects, side effects, drug interactions, and cost [18, 24]. AASM does not recommend one particular drug over another as there are few clinical trials comparing the efficacy of specific medications [24].

When pharmacotherapy is used, patients should be assessed regularly to evaluate treatment response, potential side effects, and the ongoing need for medications. Medications should be used at the lowest effective dose and tapered whenever possible [18]. The frequency of administration can be nightly or intermittently, and an assessment 2–4 weeks after treatment initiation is usually appropriate to decide whether to continue with the current therapy [18]. Chronic pharmacotherapy should be reserved for patients who are followed regularly, continue to demonstrate benefits, and were properly screened for contraindications and when nonpharmacologic therapies are not effective or not an option [24].

AASM recommends against the use of trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, and valerian due to lack of evidence of clinically significant benefit. Data were insufficient for AASM to provide clinical recommendations for the use of several other medications that are used off-label in the treatment of insomnia, including gabapentin and quetiapine [24]. Benzodiazepines and Z-drugs should be avoided in the elderly due to increased risks (e.g., cognitive impartment, delirium, falls) [28]. Over-the-counter agents such as antihistamines are often used as self-remedies; however, they have the potential for serious side effects including anticholinergic symptoms [18].

Clinical Pearls

- Insomnia is a clinical diagnosis made when a patient presents with complaints of initiating or maintaining sleep, or waking up too early despite adequate opportunity and

circumstances for sleep, which results in some form of daytime impairment.
- A thorough medication review should be completed, as many medications may impact a patient's sleep pattern.
- All patients should undergo a clinical evaluation to identify medical or psychiatric conditions potentially contributing to insomnia and should maintain a sleep diary for 2 weeks as part of the diagnostic evaluation.
- No diagnostic test needs to be performed to diagnose insomnia; however, polysomnography may be indicated if a breathing or movement disorder is suspected.
- Behavioral and psychological interventions are recommended as first-line treatment of chronic insomnia, particularly CBT-I.
- If patients are unable to participate in behavioral and psychological interventions, or if these are ineffective, then pharmacologic methods are recommended. Medications may be used as first-line treatment of short-term insomnia.

Do Not Miss This!
- Cognitive behavioral therapy for insomnia is the first-line treatment for insomnia. It is effective, provides long-term benefits, and reduces the need for medications.

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Chapter 36
Memory Loss and Cognitive Impairment

Jarrod A. Carrol and Zaldy S. Tan

Brief Introduction

Memory loss and cognitive impairment become more common with increasing age and as the number of persons aged 65 years and older continues to rise (projected to be 25% of US population by 2040), so too does the need for evaluation and management of cognitive issues in the ambulatory setting. Early diagnosis and timely intervention for probable dementia has several benefits including early initiation of treatment, institution of safety measures, and provision of caregiver support and training. This section will outline the evidence-based evaluation, differential diagnosis, and management of memory loss and cognitive impairment.

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Key H&P/Decision-Making

While the United States Preventive Services Task Force (USPSTF) does not currently recommend routine screening of asymptomatic patients for cognitive impairment (2020 USPTF Panel recommendation) [1], many consider it best practice for providers to ask their older patients if they are experiencing memory and cognitive difficulties. Additionally, since some patients with cognitive impairment may lack awareness or insight into their loss, primary care providers need to be vigilant for the appearance of subtle signs of cognitive impairment. Some possible signs of memory loss and cognitive impairment include poor recall of recent events, medication nonadherence, change in performance of activities of daily living, and missed appointments.

It is important to distinguish probable dementia from normal cognitive aging, which is characterized by certain cognitive changes—such as speed of information processing and retrieval—that tend to occur with increasing age. At times distinguishing between normal cognitive aging and early dementia can be challenging. It may be helpful to view memory loss over a continuum spanning from normal aging to dementia, with mild cognitive impairment (mild neurocognitive disorder [NCD]) somewhere in between the two ends of the memory spectrum.

Gathering information effectively about deficits is the first step to identify a possible problem.

NW-CALMS is a mnemonic that can help collect and organize the history and background of the patient's memory loss.

- What is the ***N****ature* of the change in memory/cognition?
  - Memory: retrograde memory loss, anterograde memory loss, short-term memory loss, long-term memory loss.
  - Language: expressive language, receptive language, anomia.
  - Visuospatial: problems with pattern recognition, getting lost in familiar places.
  - Executive functioning: planning and sequencing, managing finances, affairs.

- ***When*** was the change in memory/cognition first observed?
  - Onset: when was the last time the person was perceived to be at their usual level of cognitive functioning?
- What is the ***C****ourse* of the change?
  - Fluctuating, intermittent vs gradual progressive vs rapidly progressive cognitive decline.
- Has there been any change in performance of *Activities* of Daily Living (***A****DLs*)/Instrumental activities of daily living (IADLs)?
  - Be sure to differentiate between functional decline secondary to cognitive impairment and other causes of functional impairment (e.g., stroke with residual weakness that prevents independence with ADLs or iADLs).
- Has there been any recent change in *Life situation*, *Mood*, or *Status* of health?
  - Must rule out potential confounding factors that can impact cognitive function, such as recent illness, depression, and major life changes (e.g. loss of loved one).

If possible, obtain collateral information from family and friends of patients as they may be able to provide additional information on the onset of memory loss and type/extent of deficits. In some cases, these key contributors may be the initial source of information in patients who may not be aware of their deficits [2].

Any patient with possible cognitive impairment must be assessed for potential confounders such as depression. The following are useful tools that have been validated to identify depression in the primary care setting. The Physician Health Questionnaire (PHQ) 2 is often used in primary care settings as a quick assessment for depression [3]. If the patient screens positive for *either* question, then complete the PHQ-9 (PHQ-2 plus 7 additional questions). Of note, cognitive status should be considered when using the PHQ as a depression screener due to decreased specificity in geriatric patients with cognitive impairment.

The Geriatric Depression Scale (GDS) [4] is another screening tool that has been validated in older adults. The GDS is formatted with yes/no questions which may be easier

for some patients. These screening tools can be administered in various ways to fit the patient and the practice. The tools can be sent in the mail prior to the visit for the patient to complete. Alternatively, the patient can be assisted by a nurse or other staff member asking the questions and completing the screening tool or the patient can try to complete on their own during the visit and the provider can review with the patient.

Cognitive assessment screening tools are critical in the assessment of cognitive function [5]. The following table (Table 36.1) are validated tools that are easily used in a primary care setting.

These are screening tools only with general score cutoffs regarding cognitive functioning. However, changes in the patient's functional status must be considered when evaluating a patient for cognitive impairment. For rare cases where there is incongruence between functional status and assessment performance (e.g., MoCA score of 13 with full independence in ADLs and iADLs), further neuropsychological testing could be warranted.

Neuroimaging is often obtained during the evaluation of cognitive impairment [9]. Computed tomography (CT) scan of the brain without contrast is typically the first step done in the primary care setting. It provides a general view of brain anatomy. It can detect generalized atrophy, space-occupying lesion, and previous large territory infarcts and visualize subdural hematoma and stroke.

Magnetic resonance imaging (MRI) of the brain without contrast is more specific and can give information on cerebral brain volume, specific areas of atrophy (i.e., hippocampal in AD), white matter changes, and smaller infarcts (i.e., vascular dementia, mixed dementia).

Further evaluation for abnormal metabolism/activity is typically reserved for differentiating between types of dementia and not used for routine diagnosis. In the appropriate patient the positron emission tomography (PET) scan or fluorodeoxyglucose PET (FDG-PET) scan can be used. PET identifies areas of reduced brain activity. FDG-PET directly measures brain metabolism by measuring glucose uptake in parts of the brain (decreased uptake in temporal and parietal areas in AD; decreased uptake in frontal and temporal areas in frontotemporal dementia).

Table 36.1 Cognitive screening tools

Screening tool	Time for administration	Domains tested	Scoring	Sensitivity/ Specificity in detecting dementia	Advantages (A)/ disadvantages (D)
Mini-Cog [6]	~ 3 min	Memory, construction	Total score = word recall score (3 possible points) + clock draw score (2 possible points). A total score of 3 or greater indicates lower likelihood of dementia but does not rule out some degree of cognitive impairment	Sensitivity: 99% Specificity: 93%	A: Quick screening tool. D: Some individuals with clinically meaningful cognitive impairment will score within normal limits.
Mini mental state examination (MMSE) [7]	7–10 min	Orientation, attention, comprehension, memory, language, construction	A MMSE score of less than or equal to 23 is generally accepted as indicating cognitive impairment	Sensitivity: 84% Specificity: 78%	D: Poor sensitivity in MCI and difficulty detecting changes in severe dementia

(continued)

Table 36.1 (continued)

Screening tool	Time for administration	Domains tested	Scoring	Sensitivity/ Specificity in detecting dementia	Advantages (A)/ disadvantages (D)
Montreal cognitive assessment (MOCA) [8]	10–15 min	Executive function, visuospatial, naming, memory, abstraction, language, attention, orientation	A MOCA score equal to or less than 25 is generally agreed on as being suggestive of cognitive impairment	Sensitivity: 87% Specificity: 100%	A: Increased sensitivity with diagnosing MCI. Available in multiple languages. D: Time to administer so usually not done in primary care

Differential Diagnosis

Various medical, neurologic, and psychiatric conditions can affect memory and cognition. Practitioners must approach the initial evaluation of memory loss with a broad differential as it can be the presenting symptom of a variety of conditions. The following conditions may present with memory change:

- Depression

  Elderly patients with depression may present with a syndrome of cognitive impairment resembling dementia that subsides after remission of depression [2]. Therefore, it is necessary to screen for depression and treat if present as it may be a reversible cause of the cognitive impairment (previously described as pseudodementia).
- Delirium

  Delirium is defined as an acute alteration of consciousness, characterized by inattentiveness which can often present as memory loss. Delirium typically has a reversible cause (e.g., infection), but even after identifying and addressing the cause, delirium can persist for days, weeks, or months before complete resolution occurs. Delirium can present with hyperactive and hypoactive forms. Recognition is critical as there is an increased risk of morbidity and mortality with delayed diagnosis and treatment. Patients with underlying dementia are at increased risk for delirium, so it is important for patients to be screened for cognitive impairment once delirium has resolved [2].
- Normal-Pressure Hydrocephalus (NPH)

  In this condition patients may present with a triad of urinary incontinence, memory loss, and falls [10]. Neuroimaging shows enlarged ventricles. With lumbar puncture there may be an improvement in symptoms but possibly not complete resolution of memory symptoms.
- Hypothyroidism

  The thyroid-stimulating hormone (TSH) should always be checked in the initial evaluation of patients with cognitive impairment as hypothyroidism and hyperthyroidism can cause symptoms of cognitive impairment [11].

- Vitamin B12 Deficiency

  Memory loss related to B12 deficiency can present with or without neuropathic complaints or hematological abnormalities. Vitamin B12 levels should be checked in the initial evaluation of cognitive impairment [12].
- Sleep Impairment or Related Disorders

  Insomnia can be associated with cognitive decline [13] and untreated obstructive sleep apnea (OSA) can also present with symptoms of MCI or dementia [14].
- Medication Side Effects

  There are many medications associated with somnolence or that have anticholinergic side effects and may cause cognitive effects. These medications are commonly found on BEERS list which is a regularly updated list of medications considered to be inappropriate or to be used with caution in the elderly [15]. Clinicians must always consider polypharmacy as a possible cause of cognitive problems or delirium. Psychoactive medications and drug to drug interactions may result in forgetfulness or confusion.
- Mild Cognitive Impairment (MCI)

  MCI is noted as a mild neurocognitive disorder in DSM-V (abbreviated DSM-5) [16]. With MCI, there is a decline in memory and cognition, objectively demonstrated via testing but without functional impairment and therefore no impact on patient independence. It is further classified as amnestic (significant deficits in short-term memory) or nonamnestic MCI. Patients with MCI can revert to normal cognition (rare), remain stable for years, or progress to dementia [17]. There is an increased risk of progression to AD if the patient has amnestic MCI.
- Dementia

  There are various types of dementia with Alzheimer's disease being the most common form. The following table (Table 36.2) summarizes different types of dementia.

Table 36.2 Types of dementia

Type of dementia	Key fact	Temporal course	Neuropathology
Alzheimer's disease	Most common form, 50–60% of cases	Gradual onset of symptoms, primarily memory loss	Cortical atrophy, hippocampal atrophy, tau protein
Vascular	Second most common. Common in patients with vascular risk factors	Commonly abrupt onset and stepwise progression, but can be slow progressive with small-vessel disease	Ischemic, hemorrhagic, or hypoxic lesions
Parkinson's dementia	Typically have parkinsonism features	Parkinson's disease for many years prior to onset of cognitive decline	Loss of dopamine neurons in the substantia nigra
Lewy body dementia	Typically patients have visual hallucinations and REM sleep behavior disorders early in course	Cognitive complaints appear before or around same time as movement disorder symptoms	Lewy bodies

(continued)

Table 36.2 (continued)

Type of dementia	Key fact	Temporal course	Neuropathology
Frontotemporal	Typically earlier onset (<65 years old)	Marked personality changes. Multiple forms including behavioral variant, semantic, progressive nonfluent aphasia, FTD with motor neuron disease	Tau protein

Dementia (DSM-5: major neurocognitive disorder [16])
Other less common forms: alcohol-related dementia, HIV dementia, Prion/Creutzfeldt-Jakob disease, Huntington's disease

Treatment

There are multiple medications that have been approved for the management of dementia. The following table (Table 36.3) summarizes medications approved.

In the primary care setting, evaluation of memory loss can potentially be a daunting task. The following figure (Fig. 36.1) provides a workflow for evaluation of memory loss.

TABLE 36.3 Medications approved for the management of dementia

Drug class	Mode of action	Agents/dosing	Common side effects
Acetylcholinesterase Inhibitors	Acts at the synaptic cleft by reversibly inhibiting acetylcholinesterase, thereby increasing levels of the neurotransmitter acetylcholine	Donepezil—5 mg daily × 4 weeks, titrate to 10 mg daily Galantamine—4 mg BID (or 8 mg extended-release [ER] QD) for 4 weeks, titrate to 8 mg BID (or 16 mg ER QD long-acting) for 4 weeks, and then 12 mg BID (or 24 mg ER QD long-acting) Rivastigmine—1.5 mg BID for 4 weeks, titrate to 3 mg BID for 4 weeks and then 4.5–6 mg BID *or* rivastigmine (Exelon) transdermal 4.6 mg/24 h QD patch for 4 weeks, titrate to 9.5 mg/24 h QD patch, and then 13.3 mg/24 h QD patch	Gastrointestinal intolerance (nausea, vomiting, diarrhea, anorexia), bradycardia, and vivid dreams
NMDA receptor antagonist	Blocks glutamate at NMDA receptor	Memantine—Start 5 mg QAM for 1 week and then 5 mg BID for 1 week, and then 10 mg QAM and 5 mg QPH for 1 week, and then 10 mg BID; *or* Memantine (Namenda) XR 7 mg QAM for 1 week, and then increase to 14 mg QAM 1 week, and then increase to 21 mg QAM for 1 week, and then 28 mg QAM	Confusion, drowsiness

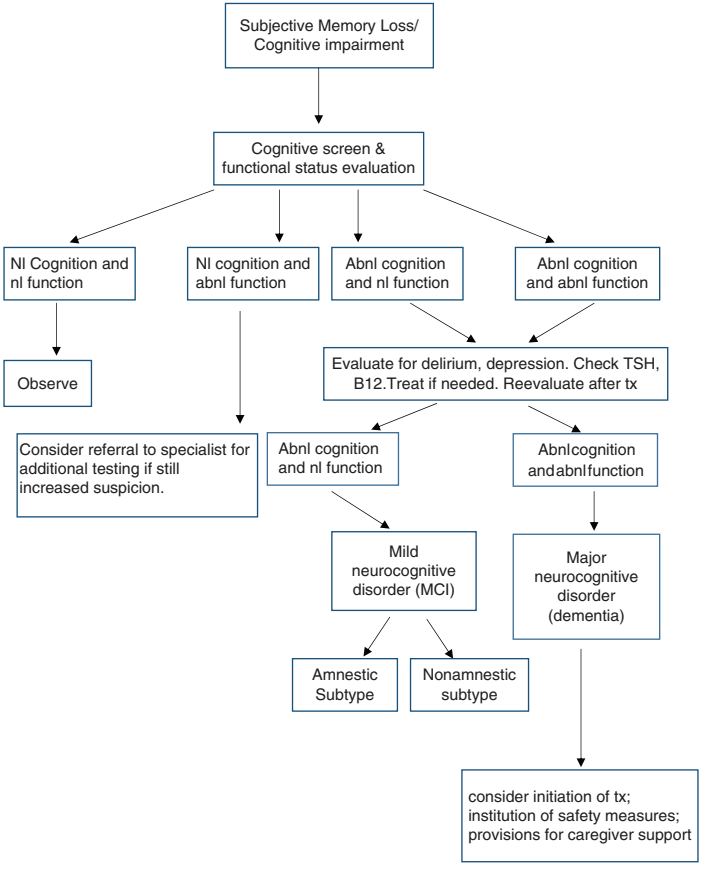

Figure 36.1 Workflow for evaluation of memory loss

Key Points

Clinical Pearls

- Patients with depression can present with memory loss. Treating depression may result in reversal of memory loss but depression can also coexist with mild cognitive impairment or dementia.
- Sleep disturbances can impact cognition and present as memory loss.

- Be cautious of diagnosing mild cognitive impairment or dementia in the acute hospital setting as presentation could be confounded by delirium. With resolution of delirium (days to months), patient should be screened for cognitive impairment.
- Diagnosis involves assessment of subjective (patient and collateral information) and objective (cognitive screening tools) information in the context of the patient's functional status.

Do Not Miss This!

- Review medication list for drugs that can impair cognition.
- Assess for mood disorders, delirium, and sleep disorders.
- Screen for hypothyroidism and B12 deficiency.
- Look for coexisting movement disorders (tremor, bradykinesia, shuffling gait) during the physical exam. Be sure to document timing of onset of movement disturbances in relation to onset of memory complaints (differentiating PDD and LBD).

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