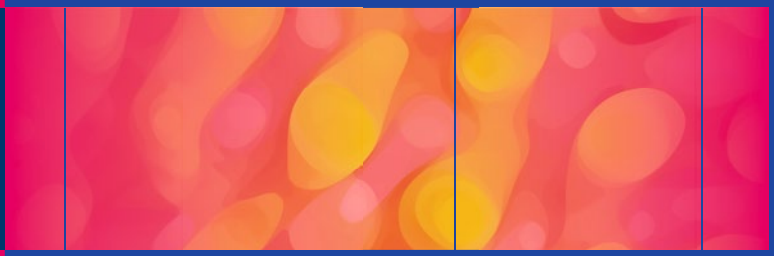
Elana Sydney · Eleanor Weinstein
Lisa M. Rucker *Editors*



Handbook of Outpatient Medicine

Springer

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ISBN 978-3-319-68378-2 ISBN 978-3-319-68379-9 (eBook)
https://doi.org/10.1007/978-3-319-68379-9

Library of Congress Control Number: 2017960768

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Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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 too 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 was to provide such a roadmap for the common problems that present themselves to the outpatient adult provider.

This book is organized into two main 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 second section focuses 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 commonly included in textbooks are covered here as well. These topics include obesity, sleep apnea, and hair loss. 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 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.

Bronx, NY, USA

Elana Sydney, MD
Eleanor Weinstein, MD
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Abbreviations

A1c	Hemoglobin A1c
AC	Acromioclavicular
ABRS	Acute bacterial rhinosinusitis
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ARS	Acute rhinosinusitis
ATN	Acute tubular necrosis
AGIs	Alpha-glucosidase inhibitors
ACC	American College of Cardiology
AHA	American Heart Association
ARBs	Angiotensin receptor blockers
ACEIs	Angiotensin-converting enzyme inhibitors
AHI	Apnea-Hypopnea index
AVM	Arteriovenous malformation
ASA	Aspirin
ASCVD	Atherosclerotic cardiovascular disease
BPH	Benign prostate hypertrophy
BDZRA	Benzodiazepine Receptor Agonist
CURB 65	Confusion, Uremia, Respiratory distress, Blood pressure<90/60, age 65
CVD	Cardiovascular Disease
CSA	Central Sleep Apnea
CXR	Chest X ray

CDH	Chronic daily headache
CKD	Chronic kidney disease
CVT	Chronic venous thrombosis
CBT	Cognitive behavioral therapy
CI	Confidence interval
CAD	Coronary artery disease
CP	Chest pain
DVT	Deep vein thrombosis
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase 4
ER	Emergency room
ESRD	End-stage renal disease
FENa	Fractional excretion of sodium
FeUrea	Fractional excretion of urea
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GAS	Group A Streptococcus
HC	Hemicranias continua
HTN	Hypertension
HRS	Hepatorenal syndrome
HDL-c	High-density lipoprotein cholesterol
H&P	History and physical
HIV	Human immunodeficiency virus
IV	Intravenous access
IVFs	Intravenous fluids
LFTs	Liver function tests
LDL-c	Low-density lipoprotein cholesterol
LP	Lumbar puncture
MO	Medication overuse
NSF	Nephrogenic systemic fibrosis
NSAIDs	Non-steroidal anti-inflammatory drugs
NTG	Nitroglycerin
OHS	Obesity hypoventilation syndrome
OSAHS	Obstructive sleep apnea/hypopnea syndrome
OCST	Out of center sleep testing
O_2	Oxygen
PH	Paroxysmal hemicranias
PICC	Peripherally inserted central catheters

PSG	Polysomnography
PAP	Positive airway pressure
PPIs	Proton pump inhibitors
PE	Pulmonary embolism
ROM	Range of motion
RADT	Rapid antigen detection testing
RBCs	Red blood cells
RR	Relative risk
SUNCT	Short lasting unilateral neuralgiform headache
SDB	Sleep disordered breathing
SGLT-2	Sodium-glucose transporter 2
SNP	Split night polysomnography
SAH	Subarachnoid hemorrhage
SDH	Subdural hematoma
SVC	Superior vena cava
TMJ	Temporal mandibular joint
TTH	Tension-type headache
TZD	Thiazolidinediones
TSH	Thyroid stimulating hormone
TTE	Transthoracic echo
TAC	Trigeminal autonomic cephalalgia
T1D	Type 1 diabetes
T2D	Type 2 diabetes
US	Ultrasound
UA	Urinalysis
USPSTF	US preventive services task force
VLDL-c	Very low-density lipoprotein cholesterol
WBCs	White blood cells

Part I
General Considerations

Chapter 1
Screening/Physical Exam/ Health Maintenance

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 thoughtful screening to better inform the physical examination and health maintenance planning.

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_1

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.

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

The US Preventive Services Task Force [1] (USPSTF) is an independent panel of experts in primary care and prevention. This panel systematically reviews the literature for evidence of effectiveness and develops recommendations for clinical preventive services. The USPSTF highlights over 50 "A-" and "B-"rated recommendations based on a patient's gender, age, and certain risk factors (Table 1.1) [2]. 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 1.2) [3]. 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 as well as other similar panels makes recommendations for screening for behavioral conditions and risky behaviors such as depression [4], sedentary lifestyle, and alcohol use [5]. These recommendations encourage conversations about issues that are very relevant to a patient's health and the care delivered.

TABLE 1.1 2016 Modified USPSTF A and B recommendations

Topic	Description	Grade	Release date of current recommendation
Bacteriuria screening: pregnant women	The USPSTF recommends screening for asymptomatic bacteriuria with urine culture in pregnant women at 12–16 weeks' gestation or at the first prenatal visit, if later	A	July 2008
Blood pressure screening: adults	The USPSTF recommends screening for high blood pressure in adults aged 18 years or older. The USPSTF recommends obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment	A	October 2015
Cervical cancer screening	The USPSTF recommends screening for cervical cancer in women ages 21–65 years with cytology (Pap smear) every 3 years or for women ages 30–65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years	A	March 2012

(continued)

TABLE 1.1 (continued)

Topic	Description	Grade	Release date of current recommendation
Colorectal cancer screening	The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years	A	June 2016
Folic acid supplementation	The USPSTF recommends that all women planning or capable of pregnancy take a daily supplement containing 0.4–0.8 mg (400–800 μg) of folic acid	A	May 2009
Gonorrhea prophylactic medication: newborns	The USPSTF recommends prophylactic ocular topical medication for all newborns for the prevention of gonococcal ophthalmia neonatorum	A	July 2011
Hepatitis B screening: pregnant women	The USPSTF strongly recommends screening for hepatitis B virus infection in pregnant women at their first prenatal visit	A	June 2009
HIV screening: nonpregnant adolescents and adults	The USPSTF recommends that clinicians screen for HIV infection in adolescents and adults ages 15–65 years. Younger adolescents and older adults who are at increased risk should also be screened	A	April 2013

HIV screening: pregnant women	The USPSTF recommends that clinicians screen all pregnant women for HIV, including those who present in labor who are untested and whose HIV status is unknown	A	April 2013
Rh incompatibility screening: first pregnancy 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
Tobacco use counseling and 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 adults who use tobacco	A	September 2015
Tobacco use counseling: pregnant women	The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco	A	September 2015

(continued)

TABLE 1.1 (continued)

Topic	Description	Grade	Release date of current recommendation
Syphilis screening: nonpregnant persons	The USPSTF recommends screening for syphilis infection in persons who are at increased risk for infection	A	June 2016
Syphilis screening: pregnant women	The USPSTF recommends that clinicians screen all pregnant women for syphilis infection	A	May 2009
Abdominal aortic aneurysm screening: men	The USPSTF recommends one-time screening for abdominal aortic aneurysm by ultrasonography in men ages 65–75 years who have ever smoked	B	June 2014
Alcohol misuse: screening and counseling	The USPSTF recommends that clinicians screen adults age 18 years or older for alcohol misuse and provide persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce alcohol misuse	B	May 2013

Aspirin preventive medication: adults aged 50–59 years with a ≥ 10% 10-year cardiovascular risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50–59 years who have a 10% or greater 10-year cardiovascular 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
BRCA risk assessment and genetic counseling/testing	The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (*BRCA1* or *BRCA2*). Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing	B	December 2013

(continued)

TABLE 1.1 (continued)

Topic	Description	Grade	Release date of current recommendation
Breast cancer preventive medications	The USPSTF recommends that clinicians engage in shared, informed decision-making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene	B	September 2013
Breast cancer screening	The USPSTF recommends screening mammography for women, with or without clinical breast examination, every 1–2 years for women age 50–74 years	B	January 2016
Breastfeeding interventions	The USPSTF recommends providing interventions during pregnancy and after birth to support breastfeeding	B	October 2016
Chlamydia screening: women	The USPSTF recommends screening for chlamydia in sexually active women age 24 years or younger and in older women who are at increased risk for infection	B	September 2014

Depression screening: adults	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
Diabetes screening	The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40–70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity	B	October 2015
Falls prevention in older adults: exercise or physical therapy	The USPSTF recommends exercise or physical therapy to prevent falls in community-dwelling adults age 65 years and older who are at increased risk for falls	B	May 2012
Falls prevention in older adults: vitamin D	The USPSTF recommends vitamin D supplementation to prevent falls in community-dwelling adults age 65 years and older who are at increased risk for falls	B	May 2012

(continued)

TABLE 1.1 (continued)

Topic	Description	Grade	Release date of current recommendation
Gestational diabetes mellitus screening	The USPSTF recommends screening for gestational diabetes mellitus in asymptomatic pregnant women after 24 weeks of gestation	B	January 2014
Gonorrhea screening: women	The USPSTF recommends screening for gonorrhea in sexually active women age 24 years or younger and in older women who are at increased risk for infection	B	September 2014
Healthy diet and physical activity counseling to prevent cardiovascular disease: adults with cardiovascular risk factors	The USPSTF recommends offering or referring adults who are overweight or obese and have additional cardiovascular disease (CVD) risk factors to intensive behavioral counseling interventions to promote a healthful diet and physical activity for CVD prevention	B	August 2014
Hepatitis B screening: nonpregnant adolescents and adults	The USPSTF recommends screening for hepatitis B virus infection in persons at high risk for infection	B	May 2014

Hepatitis C virus infection screening: adults	The USPSTF recommends screening for hepatitis C virus (HCV) infection in persons at high risk for infection. The USPSTF also recommends offering one-time screening for HCV infection to adults born between 1945 and 1965	B	June 2013
Intimate partner violence screening: women of childbearing age	The USPSTF recommends that clinicians screen women of childbearing age for intimate partner violence, such as domestic violence, and provide or refer women who screen positive to intervention services. This recommendation applies to women who do not have signs or symptoms of abuse	B	January 2013
Lung cancer screening	The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults ages 55–80 years who have a 30 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	December 2013

(continued)

Table 1.1 (continued)

Topic	Description	Grade	Release date of current recommendation
Obesity screening and counseling: adults	The USPSTF recommends screening all adults for obesity. Clinicians should offer or refer patients with a body mass index of 30 kg/m^2 or higher to intensive, multicomponent behavioral interventions	B	June 2012
Osteoporosis screening: women	The USPSTF recommends screening for osteoporosis in women age 65 years and older and in younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors	B	January 2012
Preeclampsia prevention: aspirin	The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia	B	September 2014

Sexually transmitted infections counseling	The USPSTF recommends intensive behavioral counseling for all sexually active adolescents and for adults who are at increased risk for sexually transmitted infections	B	September 2014
Skin cancer behavioral counseling	The USPSTF recommends counseling children, adolescents, and young adults ages 10–24 years who have fair skin about minimizing their exposure to ultraviolet radiation to reduce risk for skin cancer	B	May 2012

(continued)

Table 1.1 (continued)

Topic	Description	Grade	Release date of current recommendation
Statin preventive medication: adults ages 40–75 years with no history of CVD, 1 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 ages 40–75 years; (2) they have 1 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 require universal lipids screening in adults ages 40–75 years	B	November 2016
Tuberculosis screening: adults	The USPSTF recommends screening for latent tuberculosis infection in populations at increased risk	B	September 2016

TABLE 1.2 USPTF grade definitions

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 Statment	The USPSTF concludes that the current evidence is insufficent 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 recomendation statment. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms

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, and substance misuse. 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 have been well studied [6, 7]. 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 [8, 9]. 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 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 [10, 11].

Best practices when communicating with patients guide us to start off 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/misuse. Through the process known as screening, brief intervention, and referral to treatment (SBIRT) for substance misuse [12], 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.

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 have been related to an increased number of false positives, leading to further invasive investigations that can exponentially increase the degree of risks to patients.

One example of this is the prostate-specific antigen (PSA) blood test for detection of prostate cancer. 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") [13]. 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 [14, 15]. The evolution of this discussion and research has deemed that the benefits of PSA testing do not outweigh the harms.

Conversely, there has been a paradigm shift in the thinking and evidence around alcohol misuse screening, moving from the CAGE to the AUDIT questionnaire [16]. 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 [17], yet it failed to optimally identify current heavy drinking [18]. 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 as well as abusive use of substances.

Key History and Physical Exam

While the concept of the comprehensive physical exam in practice remains controversial [19, 20], few could dispute the value it holds as an opportunity to discover vital clues to diagnose [21] and build trust and rapport with a patient [22, 23]. 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 [24, 25] 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 [26–28].

Examinations can be comprehensive "head to toe," systematically following the review of systems and/or more focused and based on the presenting complaint. It is fundamental that the physical exam be utilized for screening, investigation, and/or for confirmation of diagnostic possibilities. For example, a presentation of dizziness may trigger the clinician to complete certain focused examinations to better understand and investigate potential factors contributing to the patient's complaint. Dizziness can be classified into four main types: vertigo, disequilibrium, presyncope, or lightheadedness, and one of the main goals of the physical examination is to attempt to reproduce the patient's dizziness in the office [29]. A cardiac examination should be performed for all patients complaining of dizziness, but specific nonroutine components of the physical examination can play a large role in investigating this complaint. Examples include measurement of blood pressure in various positions to rule in/out orthostatic hypotension [30], the Dix-Hallpike maneuver to elicit nystagmus [31], the Romberg test, and observation of gait [32, 33], and if hyperventilation syndrome is suspected, the diagnosis can be confirmed by having the patient rapidly take deep inhalations and exhalations [34].

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. Capitalizing on the rapport and trust 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.

Vaccinations

The Centers for Disease Control and Prevention (CDC) recommends vaccinations from birth through adulthood to provide a lifetime of immunity [35] 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 [36]. 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., influenza, human papillomavirus (HPV) [37], pertussis, pneumococcal disease, etc.), vaccination compliance remains low [38, 39]. 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 [40].

In October of 2016, an updated version of the Advisory Committee on Immunization Practices (ACIP) vaccination table was approved [41]. 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 [42, 43]. 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 [44].

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.
- Become familiar with tools used to screen for behavioral health issues and substance abuse. Comfortable use by the provider will help the patient respond openly.
- Learning how to focus the physical exam based on the patient's specifics as well as their presenting concerns is critical to effective encounters in the clinical setting.

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Chapter 2
Transition Care of Teens with Chronic Health Conditions

Kamala Gullapalli Cotts and Sanjay Jumani

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]. Literature reveals that at least 30% of young adults have one or more chronic conditions, and about 5% of young adults report having a disability that affects their daily life [2]. As of 2011/2012, US National Survey of Children's Health, there are an estimated nine million young adults in the USA with a chronic condition, including 1.5 million with a disability, who are transitioning from pediatrics to adult providers [3].

In 2011, the American Association of Pediatrics (AAP), American Association of Family Practitioners (AAFP), and the American College of Physicians (ACP) released a clini-

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_2

Table 2.1 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

cal report [4] containing guidelines to aid pediatricians, family practitioners, and internists in the transition of care of the adolescent **(**Table 2.1**)**. In this report, special focus was given to caring for those with special needs, and outlined the importance 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 supports needed to successfully manage their health.

Barriers in Transition Care

Barriers for AYASHCN stem from factors relating back to the patient, the provider, and community at large. Patients

themselves are somewhat unequipped to advocate for their own needs because there is relatively high parent 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-twenties. 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 multi-disciplinary 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 are often times unable to advocate for themselves 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 caregivers are concerned that young adult patients cannot independently manage their own health [9, 10]. However, many young adult patients themselves report being ready to take on 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. 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. In this survey, internists agreed with caregivers that patients may not be ready to make decisions independently and were concerned that families will not stay involved when needed. This study elicited concerns from internists, including lack of family involvement, especially for patients with intellectual disability or cerebral palsy, and the expectations of families regarding length of visits with internists. Additionally, internists felt concerns about the need to face disability and end-of-life issues at an early age and early in the doctor-patient relationship. Finally, the survey showed 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]. Also, research has shown that poor transfer of healthcare information can lead to delays in receiving adult-oriented care [17]. Pediatricians, often left without clear guidance on creating portable medical summaries, are challenged with summarizing over two decades of health problems. Internists are often left without enough information and 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 both healthcare professionals and 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 review the patient's medical history 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 (SD) 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 2.2); 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 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

Table 2.2 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, avoiding victimization
Practical deficits	Personal care activities: eating, dressing, bathing, meal preparation, telephone communication, transportation Occupational skills: organizing school and work activities, money management, job duties

requirements of a person with an intellectual disability [24]. While it is important to be aware of such scales, it is not possible or necessary for these types of assessments to be completed during the initial primary care visit. 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. Over 30% of young adults with learning disabilities drop out of high school, 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 disability are provided an individualized public school education. Transition planning can occur with the family and educators

in the Individual Education Plan (IEP) generated for many students with learning disabilities. Many states have databases to register disabled people to select individuals for services as funding becomes available.

Living Arrangement and Family Support

The internist should have an understanding of the patient's living arrangement to estimate the support the patient will require. Some patients may be living at home with their families, while others may be living independently with a case manager. Some may require additional support and will be living in a group home. It is important for the provider to be aware of the patient's living situation when working with patients. 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

All individuals with disabilities are eligible for Vocational Rehabilitation (VR) services through 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 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 39

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. 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

At the initial visit, adult providers will need a quick assessment of the decision-making capacity of the young adult with chronic disease of childhood that has transitioned to their practice. Equal to individuals in the general population, developmentally disabled adults should be entitled to exercise their legal capacity. 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, where to live and with whom, and activities to participate in during the day.

If an individual has partial decision-making capacity, there are alternatives to full guardianship that vary from state to state. These are the least intrusive measures on 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 2.3**)**. Additionally, as in the general population, 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 2.4**)**.

Table 2.3 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 accounts	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 2.4 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

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 their 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.

Local Resources

Each state has an office for intellectual/developmental disabilities. 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 working with adult patients with chronic diseases of childhood, internists have additional challenges that they might otherwise not encounter in their day-to-day practice. For example, questions of guardianship and the legal-therapeutic relationship may go unaddressed until it threatens the

care of the patient. 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. 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 vertically transmitted HIV. 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. 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. For young adults who are transitioning to adult-oriented care, patients may need additional support in finding adult subspecialists who have expertise in the management of chronic diseases of childhood. Furthermore, internists shouldn't neglect appropriate adolescent/young adult-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 and 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.

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 in general. These individuals are at more 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 anti-epileptics which increase the risk of osteoporosis [28] and phenothiazine, which can cause weight gain and QT prolongation that increases the risk for reentrant tachycardias [29].

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 [30]. For example, adults with juvenile idiopathic arthritis (JIA) are more at risk for pain, anxiety, and depression than their peers [31].

In general, there are multiple secondary and coexisting conditions seen at a higher frequency in teens with chronic conditions originating in childhood including; obesity, vision and hearing problems, hypothyroidism, congenital heart disease, gastrointestinal problems including constipation and gastroesophageal reflux disease, chronic pain, and epilepsy [32–34].

Behavioral Health

Children and young adults with chronic health conditions have a higher risk of behavioral conditions. Data links chronic disease with dysthymia [35], depression [35], and anxiety [36]. 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 2.5 outlines some commonly used screening tools for psychiatric conditions.

Anxiety

Youths with chronic disease have a higher incidence of anxiety than their peers in the general population [36]. 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

Table 2.5 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

disease tends to present with more externalizing behaviors as well as 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 extremely prevalent in persons with chronic disease [35]. Like other psychiatric conditions, young adults with chronic childhood diseases may present differently than 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.

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. [37]. Readily available resources during an initial visit can facilitate transition and improve quality of care for AYASHCN. Table 2.6 outlines some sample diseases and their long-term management.

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 health-care 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 health-care setting [41, 42]. Although disabled adolescents may have delayed puberty and are 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.

TABLE 2.6 Common comorbidities in the management of AYA with chronic diseases [38–40]

Common comorbidities/long-term management of young adults with chronic diseases of childhood	
Cerebral palsy	Contractures, scoliosis—orthopedic evaluation Constipation—aggressive bowel regimen Dysphagia/Aspiration—periodic speech and swallow evaluation Gastroesophageal reflux disease—feeding by gastrostomy tube Decubitus ulcers—assess at each visit
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 periodically Thyroid dysfunction—annual screening Visual loss (cataracts, keratoconus)—eye exam every 3 years Obesity, hypertension—annual screening
Epilepsy	Polypharmacy—evaluation of medications and side effects Sports/activity evaluation Driving evaluation—patients must be seizure free to drive
Autism spectrum disorder	Higher rates of physical conditions: allergies, asthma, gastrointestinal problems, epilepsy Higher rates of mental health conditions: ADHD, sleeping disorders, anxiety/depression

Sexual Abuse

Young men and women with invisible chronic diseases are more frequently victims of sexual abuse when compared to their typical controls [44]. 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 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 non-disabled people self-report their own quality of life [51]. The literature shows that healthcare professionals' opinion of quality of life of people with disabilities is lower than both the opinion of the general public and the disabled individual's own opinion [52]. Healthcare providers must be aware of their own potential bias when discussing treatment options for medical conditions as well as for screening procedures.

Conclusion

Most adult providers have a small number of teens with chronic health conditions transitioning to their practice; there are multiple elements in 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 medically complex primary diagnoses and numerous secondary health conditions. Coordination is required for the large number of subspecialists utilized. 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 that of *Healthy People 2020*, 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 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. Describe 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, *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

- 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 staring at the initial transition visit.
- Anticipate lapses in insurance and ensure that your patients will remain insured while under your care.
- Recognize biases in quality of life considerations that may affect care.

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Chapter 3
Home Care/Care of Elderly

Veronica M. LoFaso

Introduction

The population of the USA is rapidly aging. Currently 14.5% of the US population is over 65 years of age, and by 2040 approximately one in five persons will be over 65 years of age [1]. This demographic imperative necessitates a healthcare 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:

1. Enhancing function and promoting independence
2. Judicious use of diagnostic tests and procedures
3. Respect for patients' goals of care and health beliefs
4. Minimizing medications
5. Providing team based-interventions that involve patient, family, and caregivers

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_3

Outpatient Assessment

The evaluation of the older adult includes the usual 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. Some barriers to effective communication with older adults include:

- Sensory impairments
- Cognitive impairment
- Health literacy
- Having 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.
- The environment should be quiet 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.
- Spend time alone with the patient 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 ageist assumptions, aid in making the correct diagnosis, and obviate the need for unnecessary testing. The following should be included:
- Education
- Family makeup and dynamics, social supports
- Living situation, environmental hazards
- Work history, economic status
- Exercise, habits (smoking, alcohol)
- Spirituality, cultural beliefs
- Sexuality
- Healthcare goals, healthcare proxy, living will, end of life wishes

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 any over-the-counter medications should be reviewed.

Review of System for Older Adults

- General: weight loss, sleep disturbance, loss of energy
- HEENT: hearing loss, visual impairment, swallowing difficulties, 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.
- Musculoskeletal: arthralgia, muscle aches, swelling, weakness, back pain, mobility impairments, falls in the last year
- GYN: vaginal bleeding, prolapsed uterus
- CNS: headache, memory loss, weakness, dizziness, visual disturbances, tremor, neuropathy, gait instability
- Skin: rashes, skin breakdown, new 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
- GU: prostate exam, bladder prolapse, vaginal atrophy
- Rectal: rectal tone, hemorrhoids, rectal prolapse, fecal impaction

- Skin: new moles, pigmentation, turgor, rashes, pressure ulcers
- Neurologic: tremor, gait, weakness, reflexes, cranial nerves, tone, sensation, Romberg, cogwheel rigidity

Functional Assessment

Performing a functional assessment 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.
- Allows for monitoring response to interventions and medications
- Predicts mortality and morbidity [3, 4]
- Helps prognosticate likely outcomes from surgery or chemotherapy
- Helps identify new diagnoses
- Helps determine proper level of assistance in the home and proper housing options (Table 3.1)

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—seasonal yearly vaccine, given throughout the flu season [6]

Pneumococcal—pneumococcal 13-valent conjugate (PCV13) should be ideally given first followed by pneumococcal polysaccharide vaccine 23 (PPSV23) 1 year later. If already vaccinated with PPSV23, then wait 1 year and give PCV 13 [7].

Table 3.1 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 ophthalmologist
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), paying attention to pain, weakness, limited range of motion. Consider referral to physical therapy
Leg	Observe the patient after asking: "Rise from your chair, walk ten feet, return, sit down."	Inability to do task	Do full neurological and musculoskeletal evaluation, paying attention to strength, pain, range of motion, balance, and traditional assessment of gait. Consider referral for physical therapy

(continued)

TABLE 3.1 (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
Depression	Ask: "Do you often feel sad or depressed?"	Yes	Administer Geriatric Depression Scale. If positive (normal score, 0–10), check for antihypertensive, psychotropic, or other pertinent medications. Consider appropriate pharmaceutical or psychiatric treatment

(continued)

Table 3.1 (continued)

Target	Assessment Procedure	Abnormal Result	Suggested Intervention
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 is uncertain. Determine reasons for inability (motivation compared with physical limitation). Institute appropriate medical, social, and environmental interventions
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: "How would be able to help you in case of illness or emergency?"		List identified persons in the medical record. Become familiar with available resources for the elderly in the community

Lachs MS et al. [5]

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 [8].

Herpes zoster—not needed if patient has received chicken pox vaccine. It is a live vaccine and therefore is contraindicated in some immunocompromised individuals. The vaccine is indicated even if a patient has had shingles in the past [9].

Primary and Secondary Disease Prevention [10]

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

Calculating life expectancy can be a helpful guide when considering which interventions to institute for an older adult. See www.eprognosis.org [11].

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) [12].
- 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 [13].

Geriatric Syndromes

Geriatric syndromes are clinical syndromes commonly encountered in older adults.

Urinary Incontinence (Table 3.2)

Dementia (See Chap. 35)

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 age 65 have Alzheimer's dementia [14]. 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.

TABLE 3.2 Evaluating urinary incontinence

Type	Gender	Amount	Risk factor	Complaint	Timing	Treatment
Urge	M = F	Large	Idiopathic, poststroke, local bladder abnormalities, lesions in the inhibitory nerve pathways	Sudden need to void	Day and night (N > D)	Anti-muscarinic 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	Anti-muscarinic 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[a]	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

[a]*DHIC* detrusor hyperactivity with impaired contractility

Confusion Assessment Method (CAM)—short version [15]:

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

For 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 sedated, 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

- Review of medications
- Consider drug or alcohol ingestion or withdrawal
- Ascertain any history of psychiatric illness
- 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
- Imaging of the brain: CVA, tumor, hemorrhage
- EKG: MI, arrhythmia
- 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 dentures, 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 advisable as needed.

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 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 [16].

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 first time episode of depression.

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

   Sertraline or citalopram. **Side Effect**s: 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
   - Duloxetine: may be useful to control pain as well

3. Additional options:

   - SSRI plus buproprion
   - Augmentation of SSRI with quetiapine or aripiprazole
   - Electroconvulsive therapy: can be very effective in medication nonresponders 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 [9]. The incidence of a second fall occurring within the same year as an initial fall is 60%. The causes of falls are usually multifactorial. An evaluation for environmental and medical etiologies should be performed. Older adults presenting with a fall should be carefully queried about the circumstances, and timing of the fall as falling is often a presenting sign of medical illness [17] (Table 3.3).

Table 3.3 Assessing falls in older adults

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
ADL impairment	Medication side effects
Muscle weakness	Sensory impairments
Age > 80	Neurological disorders (Parkinson's, MS)
Vision impairment (multifocal lenses), cataracts, macular degeneration	
Environment: stairs, clutter, rugs	
Alcohol use	

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

A Careful History Is Key to Determining the Cause of a Fall. Some Useful Questions Include: [17]

1. **Can you describe the circumstances surrounding your fall?** What happened?
2. **Did you lose consciousness?** If so, this is syncope and needs a syncope evaluation.
3. **Did you feel light-headed or as if you were going to faint?** Vasovagal episode.
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**? This suggests adverse drug effect.

Examination of the Older Adult After a Fall [17]

- **Gait, balance, and mobility assessment:** detailed assessment of gait, balance, mobility, and lower extremity joint function.

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

Get Up and Go Test [18]

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; 5, severely abnormal. Score of three or more increased risk of falling.

Preventing Future Falls

- Reduce all meds to minimum needed especially 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 vision problems.
- 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. 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** [19].

Sensory Loss

Vision

Impairment in vision can have a significant impact on 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:

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:

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 3.4).

TABLE 3.4 Evaluating weight loss in older adults

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 <22Kg/m^2 Loss > 5%BW in 1 mo. Loss >10% BW in 6 mos. Low albumin or prealbumin 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

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 [22]. Identification and treatment of osteoporosis are fundamental parts of maintaining function and preventing morbidity and mortality in older adults.

Consider FRAX score (Fracture Risk Assessment Tool—WHO) for assessing 10-year probability of fracture when considering treatment. See www.shef.ac.uk/frax [16].

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. Management options include addressing sleep hygiene, adequate pain management, treating urinary symptoms, cognitive behavioral therapy, and pharmacological interventions:

- Melatonin—start at 2–4 mg.
- Trazodone—start 25–50 mg.
- Sedative hypnotics (zolpidem 5 mg, eszopiclone 1 mg)—use sparingly and with caution for falls, excess daytime fatigue, and confusion.

Advanced Care Planning

Working with patients and families to establish their 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.
- Healthcare proxy: identifying a person of trust for healthcare 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 1 in 10 older adults is a victim of elder mistreatment [23]. Types of elder mistreatment include psychological, physical, financial, and sexual abuse as well as neglect. Unfortunately only 1 in 24 cases of abuse is identified [16]. 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:

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 [24]
(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 are 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 healthcare costs. This backdrop makes home visits an appealing healthcare 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 [20] (Fig. 3.1).

Clinical Pearls

- Be aware of black box warning for cardiac events with antipsychotics.
- When using antipsychotics, follow EKG for prolongation of QTc.
- Avoid antipsychotics in Parkinson's or Lewy body dementia patients—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.

Sample House Call Checklist (Based on the INHOMESSS Mnemonic)

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):
_____
_____

FIG. 3.1 Sample house call checklist (Based on the INHOMESSS mnemonic) [21]

- In 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 adult.
- See Beers Criteria: onlinelibrary.wiley.com/doi/10.1111/jgs.1370.
- In treating insomnia, avoid diphenhydramine and benzodiazepine medications. Evaluate carefully for fall risk before prescribing any sedating medications.

Don't Miss This!

1. Minimize the use of medication whenever possible. Review the patient's 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.
2. Assessing and improving function and social supports are major focus of geriatric care.
3. Care of the older adult is best delivered by a multidisciplinary team including social work, physical and occupational therapy, mental health, and nutrition services.
4. Advanced directives and goals of care should be clarified initially and updated periodically with any change in health status.
5. 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 4
End-of-Life Care/Pain Management/Palliative

Tabitha N. Goring

Palliative care, and the medical subspecialty of Palliative Medicine, is specialized medical care for individuals living with serious and often life-threatening illness. It employs an interdisciplinary approach to provide relief from the symptoms and stress of a serious illness. The goal is to improve quality of life for both the patient and the family [1]. Palliative care can be delivered in conjunction with disease-directed (curative) care as a continuum, and toward the end of life, it transitions to hospice care. Symptoms, such as shortness of breath, constipation, nausea, pain, delirium, insomnia, and anxiety/depression, are closely managed to help improve quality of life and relieve suffering and discomfort. While the patient is the central focus of management in palliative care, the specialty recognizes the importance of providing support to the patient's caregiving unit throughout the disease process, including bereavement support.

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_4

Palliative Care vs. Hospice Care

Hospice care is a type of palliative care, but not all palliative care is hospice care. The two terms should not be used interchangeably. Hospice care is the delivery of palliative care services to someone who is terminally ill with an estimated prognosis of 6 months or less if the disease runs a normal course [2]. Both palliative care and hospice care are a multidisciplinary approach toward pain control, symptom management, and psychosocial and spiritual support for the patient and the family. Palliative care can and should be offered at anytime during a potentially life-limiting illness and can be delivered concomitantly alongside life-prolonging treatment. Palliative care is not intended to be limited to only the last 6 months of life. Once it is determined that the patient's life expectancy is <6 months, the patient can elect to enroll in the hospice benefit, at which time palliative care transitions to hospice care. Services delivered are similar, but once transitioned to hospice, medical treatments with curative intent are relinquished. Hospice care can be delivered in various care settings including the patient's home, a designated hospice facility, a nursing home, or a hospital. The word "hospice" is sometimes confusing because the term can be used to describe an actual place or a type of care. Both Medicare and some private insurance companies cover hospice services depending on the qualifying diagnosis. Most patients receiving hospice care do have cancer; however, there are multiple non-cancer qualifying diagnoses for which services are offered such as dementia, ALS, Parkinson's disease, end-stage CHF/COPD/cirrhosis, stroke, or HIV/AIDS, to name a few. Two physicians must certify the clinical need for hospice services and attest based on clinical judgment, that the patient has a less than 6-month life expectancy, if the illness takes its normal course [2]. Hospice services are multidisciplinary and should include a physician, nurse, nurse's aides, social worker, chaplaincy, nutritionist, psychologist, and other staff as deemed appropriate.

Role of the Primary Care Physician vs. Palliative Care Subspecialist Referral

Primary care physicians are well positioned to deliver effective palliative care. Palliative care specialists have special training in advanced pain management, symptom management, hospice eligibility, and bereavement. Basic pain management and symptom control can be initiated and managed without a subspecialty referral. One key goal of palliative care is to reduce emergency room visits and frequent unnecessary hospitalizations which are uncomfortable for the patient at the end of life. A palliative care subspecialty referral should be considered under the following circumstances: complex family dynamics, complicated pain management, ongoing symptomatology refractory to conventional treatments, complex goals of care, challenging end-of-life discussions, and/or in cases where the primary clinician is uncomfortable with any aspect of delivering palliative care.

Key History Components Unique to the Palliative Care Assessment

Palliative symptom
Previous palliative procedures and medications
Detailed pain assessment
Determine patient's disease awareness
Values/preferences/religion
Support system
Assessment
Goals of care and advance care planning
Disposition

Management of common palliative symptoms—shortness of breath, constipation, nausea, and pain

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 initially evaluated as any patient with SOB. Determine whether the underlying cause is reversible or can be improved by minimally invasive measures. Both medical management and surgical management may be options. Discuss the degree of work-up desired by the patient, considering extent of disease and functional status. If not clarified previously, discussions about intubation and code status should be initiated and the patient's wishes documented. Shortness of breath is a symptom that should be stabilized and managed aggressively in order to ensure the patient's comfort. Assess for reversible causes and consider referral to an inpatient facility to stabilize the respiratory status—hospital vs. inpatient hospice facility vs. continuous home care if enrolled in hospice. Reversible causes should be addressed to the extent that the patient can be returned to an acceptable baseline. Invasive procedures can be pursued if they are congruent with the patient's goals of care. In the actively dying patient, the focus is on comfort and control of the patient's respiratory drive in order to minimize labored breathing and distress. 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 O2 via this modality—if that is in keeping with the patient's goals. Opiates, including morphine, are well known to have positive effects on control of dyspnea and/or air hunger [3]. Morphine is the most commonly used opiate, but any opioid analgesic agent can be

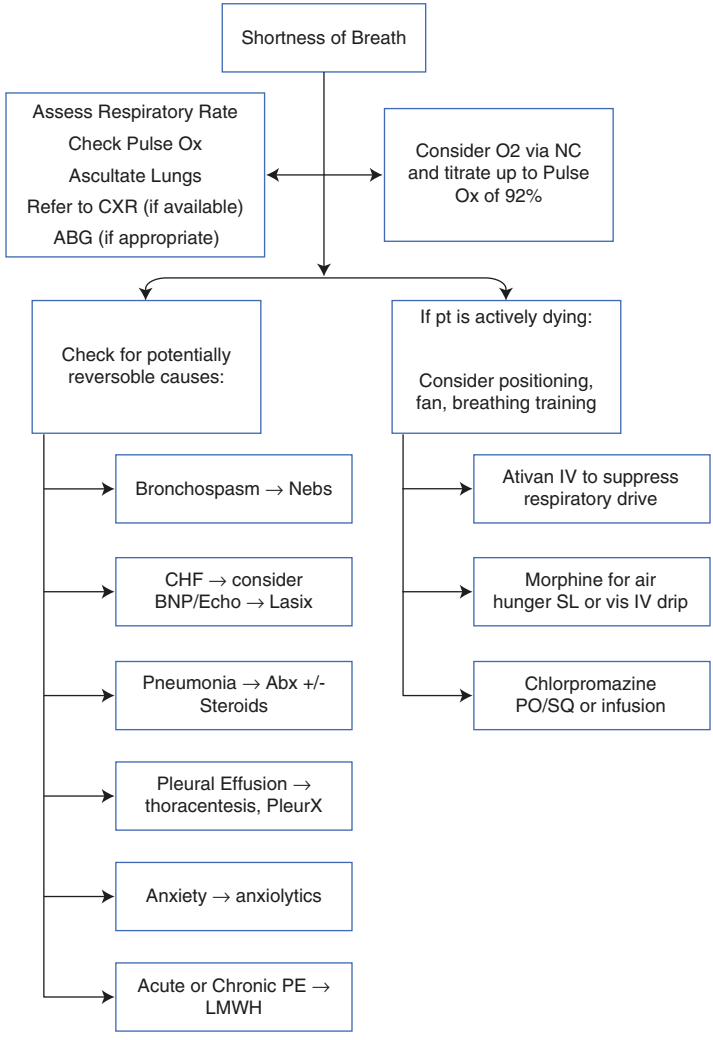

FIG. 4.1 Algorithm for shortness of breath at the end of life

administered for air hunger. Opioids can be delivered orally, sublingually, subcutaneously, transdermally, intrathecally, or via an intravenous drip (Fig. 4.1).

Constipation

Constipation can be a very uncomfortable symptom in the palliative care population and should be managed aggressively for comfort. Opioid use, chronic dehydration (poor PO intake, anorexia, vomiting, diarrhea), and limited mobility are the main factors that place this population at such high risk for constipation.

Initial evaluation includes a thorough H&P. Key history includes stool frequency, opioid use, and medication history. Key physical exam includes hydration status, a thorough abdominal exam to r/o bowel obstruction ± rectal exam to r/o stool impaction, if indicated. 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, bowel training, and/or encourage exercise. Anorectal testing, colonic transit testing, defecography, and surgery are usually too invasive and unlikely to be beneficial in the palliative care population. Biofeedback, or pelvic floor training, could be considered. Appropriate 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 [4]. Know the difference between stimulant (bisacodyl, senna) and osmotic (polyethylene glycol, lactulose, sorbitol, milk of magnesia (MOM), 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 liquids. Stimulant laxatives, for example, may cause excessive cramping. Prescribe the form most comfortable for the patient at the lowest dose to encourage a bowel movement (Fig. 4.2).

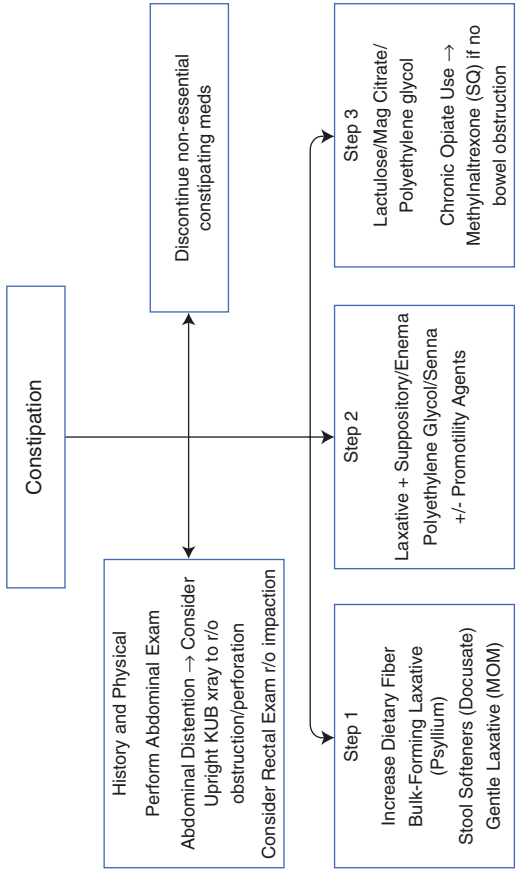

FIG. 4.2 Management of constipation in palliative care

Nausea

Nausea is an uncomfortable, subjective symptom which often precedes vomiting. Nausea/vomiting is a protective mechanism the body uses to expel toxins, unsavory food, etc. but can also be triggered by emotional causes, side effect to medications, and can originate in the CNS or from the GI tract. There are several complex neural mechanisms involved in nausea and vomiting. The areas involved include the medulla/nucleus tractus solitarius (vomiting center), cortex, chemoreceptor trigger zone (area postrema), upper GI tract, and/or labyrinths. One or more of these areas can be affected. Determining the underlying etiology of the nausea/vomiting helps the clinician to choose the appropriate medication/intervention that targets the specific receptor. Muscarinic, dopamine, histamine, serotonin, opioid, and neurokinin neurotransmitter receptors can be involved [5]. Antiemetics fall into classes that target certain receptors.

When stacking medications, choose agents with different mechanisms of action at the lowest, most effective dose and try to avoid polypharmacy. Nausea/vomiting has many causes, but in the palliative care population, it is more frequently a side effect of chemotherapy or opioid use, is related to GI obstruction/constipation, or can be as a result of CNS lesions (Fig. 4.3).

Pain

Pain management can be divided into treatment for cancer pain and non-cancer pain. A complete H&P should be performed to determine the underlying etiology of the pain, and efforts should be made to address the underlying cause. At the end of life, opioids are the mainstay of treatment and a necessary basic medication in the palliative care toolbox. Opioids can be used for all types of pain—somatic, visceral, and neuropathic as well for other symptoms such as dyspnea, cough suppression, opioid withdrawal, and diarrhea control. Existential pain should be differentiated from physical pain.

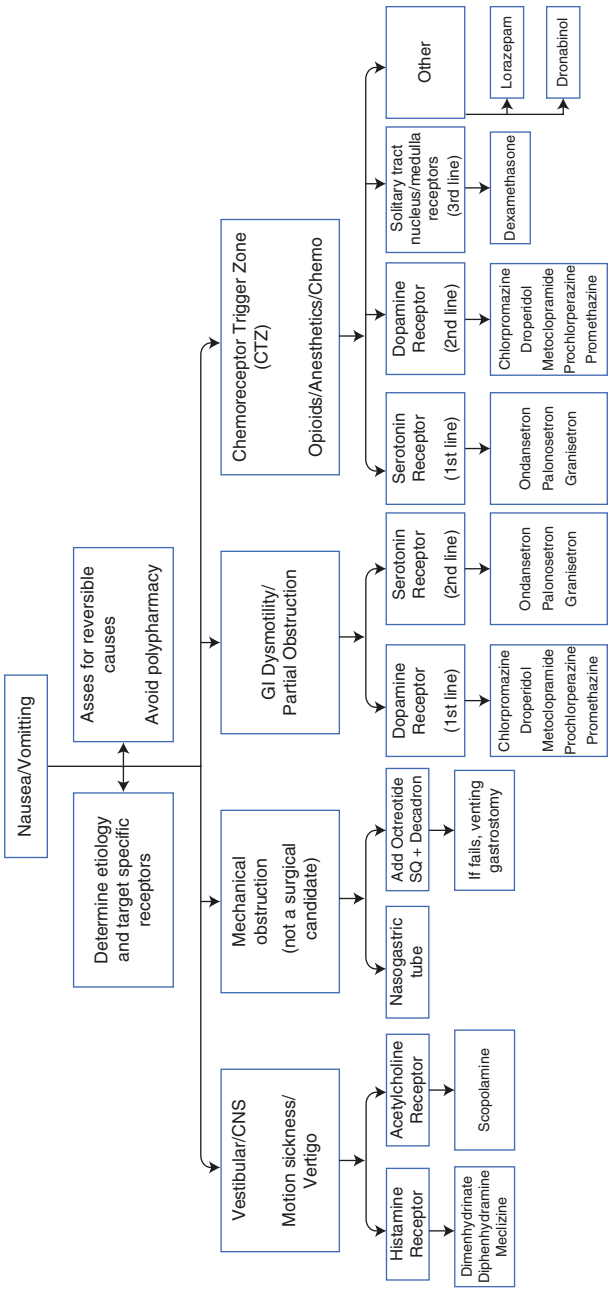

FIG. 4.3 Assessment and management of nausea and vomiting in palliative care (Modified from [5] *Flake, Z. Am Fam Physician.* 2004 Mar 1;69(5):1169–1174)

Although controversial, evidence suggests that existential pain can be managed with acetaminophen [6]. Neuropathic pain is best treated by medications with neuropathic properties such as NSAIDS, some antidepressants and anticonvulsants, and topical agents. Always consider the side effect profile of the medication and prescribe accordingly. The World Health Organization (WHO) has developed a three-step ladder for cancer pain relief [7]. When treating pain, first assess for the underlying cause. For mild pain, non-opioid pain relievers such as NSAIDS, acetaminophen, and tricyclic antidepressants, and steroids are the drugs of choice. Patients who have moderate pain may benefit from low-dose opioids, in scheduled doses ± an adjuvant pain reliever such as those given for mild pain. For more severe pain, strong opioids such as morphine, hydromorphone, oxymorphone, or fentanyl are the drugs of choice. Equianalgesic equivalent doses should be taken into account in addition to the side effect profile, metabolism/clearance of the drug, route of delivery, and cost. Strong opioids have the potential for respiratory depression, N/V, severe constipation, myoclonus, altered mental status, and urinary retention. Ketamine, an NMDA receptor blocker, can also be used for pain control in such cases as cancer-associated neuropathic pain, ischemic pain, and regional pain syndromes [8]. Anesthesia-based interventions (nerve blocks, intrathecal pump, spinal stimulators) can be attempted to address pain 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 significantly reduce or eliminate opioid use entirely. Radiation therapy is also a useful pain treatment modality, especially in cases of cancer-related bone pain (Fig. 4.4).

Advance Care Planning

Every clinician should become comfortable with the aspects of advance care planning. It is prudent to provide the patient and family with information on availability and appropriateness of

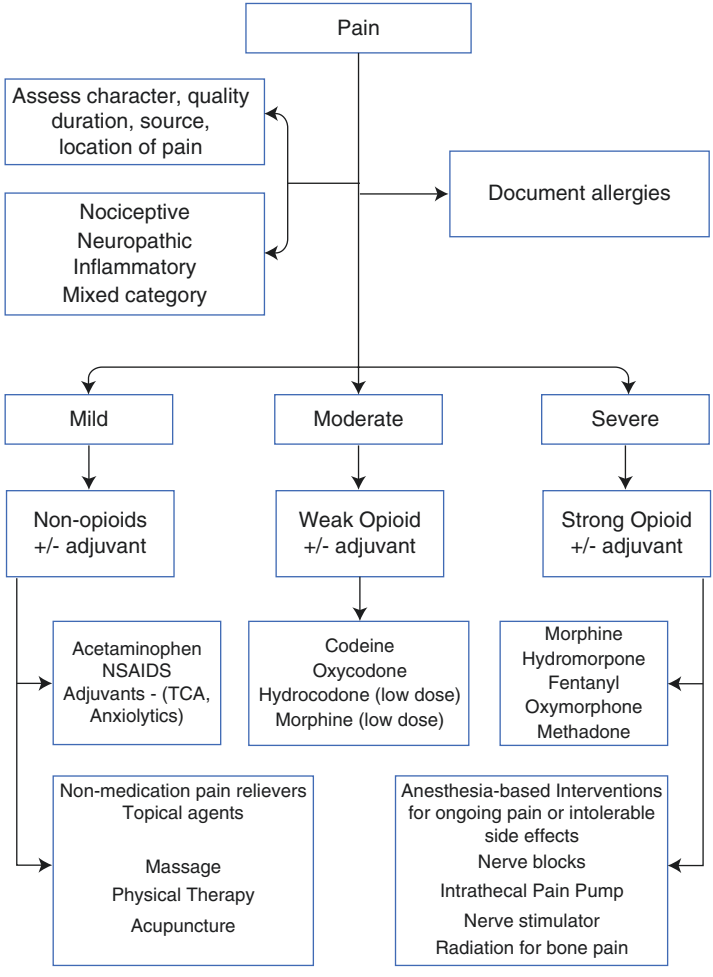

FIG. 4.4 Management of pain in palliative care (Modified from WHO Stepladder [7])

life-sustaining treatments in the event that the patient is diagnosed with a terminal illness or is nearing the end of life. Clinicians should inquire about the patient's understanding of these treatments and assess the patient's values and wishes at the end of life. Some examples of patient goals may be relief of

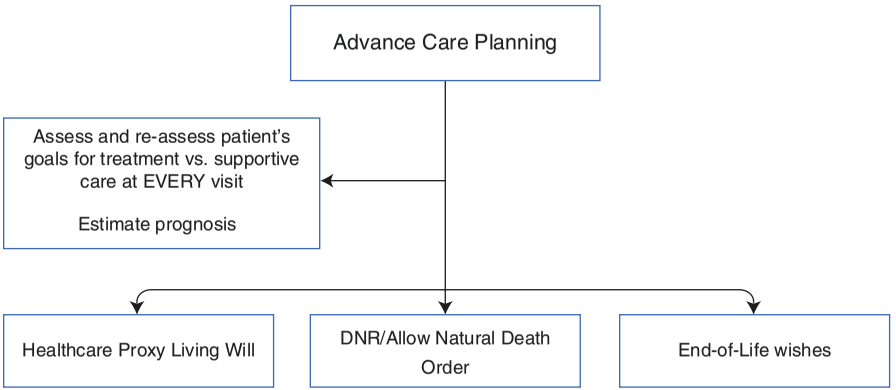

FIG. 4.5 Algorithm for advanced care planning

suffering, maintaining a certain quality of life, cure of disease, prolongation of life, avoidance of CPR, intubation, and avoidance of pain. The clinician should always inquire about patient goals rather than make assumptions about what the patient desires. Some patients have strong opinions about goals of care. Advance care planning should include some of the following:

- Inquire about "readiness" to have a goals of care (GOC) conversation with the patient.
- Inquire about past GOC discussions and review previous documentation.
- Determine the best estimate of prognosis and acknowledge uncertainty.
- Assess patient's understanding of his/her illness and prognosis, assess expectations, and encourage realistic goals.
- Inquire about family support/caregivers.
- Confirm that the patient has a healthcare proxy (HCP) and/or living will; discuss the definition of a do not resuscitate (DNR) order, and document the patient's wishes.
- Summarize wishes at end of life (EOL) and confirm agreement.
- Show empathy when discussing EOL issues.

Readdress goals at follow-up visits to make sure ongoing management is in line with evolving symptoms or progression of disease. Patients often fear abandonment by their physician at the end of life, and they should be reassured that this will not be the case (Fig. 4.5).

Hospice Care

Medicare defines four levels of hospice care [9] depending on the patient's needs:

Routine home care—is the most common level of care in the USA and is defined as care administered where the patient resides (private residence, assisted living facility, nursing facility) on an as-needed basis. This level of care can be escalated or reduced throughout the patient's course of illness.

Respite care—is short-term, usually up to 5 days of inpatient care where the patient is admitted to a contracted facility, not because of the patient's individual symptoms but solely to provide the caregiver a rest. Respite care is only provided "occasionally" in accordance with Medicare or insurance rules.
Continuous care—is care intended to support the patient and the caregiver during brief periods of crisis. Care can be provided at a minimum of 8 h but can be up to 24 h to achieve control of the acute symptom, at which time the continuous care returns to routine care. This care level is used when the individual requires predominantly skilled nursing and can be provided in the home or nursing facility.

Inpatient hospice—is care designated for those patients who require management of an uncontrolled or distressing physical symptom. Examples include pain, intractable nausea, SOB, delirium, wound care, and in cases where death is imminent and family can no longer provide care at home. The patient may be discharged from the inpatient facility to resume routine home care if he or she improves.

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.
- Shortness of breath can be managed with oxygen and opioids at the end of life.
- A bowel regimen should be prescribed along with opioids to reduce the risk of constipation.
- Try to identify the underlying etiology of nausea in order to prescribe the antiemetic that interacts with the associated receptor.
- Opioids are the mainstay of treatment for cancer pain and pain in the palliative care setting.
- Primary care physicians should feel comfortable discussing goals of care with patients.
- Advance directives should be discussed and documented in the medical record.

- There are four levels of hospice care as defined by Medicare.

Don't Miss This!

- Do not forget to evaluate for reversible causes of SOB.
- Obstruction should be ruled out in a patient with nausea/vomiting.
- Palliative care can be delivered concomitantly with disease-directed therapies.
- Rule out stool impaction in cases of chronic constipation.
- If giving multiple medications to control N/V, choose medications with different mechanisms of action.
- When treating pain, begin with non-opioid analgesics, if appropriate.
- Goals of care discussions should happen early and often if a patient has a potentially life-threatening illness.

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Chapter 5
Care of HIV Patients

Elizabeth R. Jenny-Avital

Historical Perspective and the Evolution of the Current State of the Art

In 1981, a prescient CDC report described five cases of *Pneumocystis carinii* pneumonia (now referred to as *Pneumocystis jiroveci* pneumonia, PJP) that were associated with cytomegalovirus (CMV) infection and mucosal candidiasis occurring in previously healthy gay men [1]. Soon after, the CDC reported 26 gay men with an unusual cancer, Kaposi's sarcoma, also associated with unusual infections that were indicative of defective cell-mediated immunity (PJP, CMV, toxoplasmosis, cryptococcosis) [2]. These sentinel clinical observations suggested an acquired cell-mediated immunodeficiency which became known as the acquired immunodeficiency syndrome (AIDS) in 1982. Infections, which do not occur in normal hosts but which occur by virtue of an immune defect, are termed "opportunistic infections" (OIs). The AIDS-associated OI s were associated with a markedly depressed CD4 (helper T) lymphocyte count

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_5

(<200/mm^3). With time, the spectrum of unexpected OIs and malignancies broadened as did the risk groups affected. Intravenous drug users (IDUs), hemophiliac men and women who were sexual partners of IDUs, hemophiliac or bisexual men, and their offspring also had AIDS. The human immunodeficiency virus (HIV) was isolated in the early 1980s [3, 4, 5]. Since 1985, blood products in the USA have been screened for HIV. Detailed epidemiologic studies showed that HIV was transmitted sexually, by contaminated blood and from infected mother to child during pregnancy, childbirth, or breastfeeding, but not by casual household and family contact [6].

About 2 weeks after exposure to HIV, an acute, intense viremia ensues. This may be associated with a clinical mononucleosis like seroconversion illness, consisting variably of fever, rash, sore throat, lymphadenopathy, diarrhea, and/or aseptic meningitis. Not infrequently, a concurrent sexually transmitted disease (STD) or group A beta strep in the throat obscures recognition of acute HIV. During acute HIV infection, profound CD4 cell destruction in lymphoid tissue, especially in the gut, occurs, and HIV establishes itself in its reservoirs by integrating into the host DNA of CD4-bearing cells. As an immune response supervenes, the acute HIV viremia declines to a "set point" which varies from hundreds to hundreds of thousands. The viral load set point accounts for about half of the variability of HIV progression without treatment and characterizes most of the duration of untreated infection [7, 8, 9]. Acute HIV is highly transmissible compared to chronic HIV in part due to the high-grade viremia of acute HIV but also because the viral strains detected during seroconversion are better adapted for transmission, while the viral strains detected during chronic HIV are better adapted to persistence in the host. Greater severity of seroconversion symptoms is associated with a higher subsequent set point and faster disease progression. The rationale for initiating antiretroviral therapy (ART) during acute infection is to limit the profound immunologic damage associated with acute infection, to reduce the viral reservoirs that are established as

a result of acute infection, and to treat the most infectious stage of HIV infection. This requires a high index of suspicion for acute HIV in high-risk individuals not known to be HIV positive. Suspected acute HIV infection presents an opportunity to initiate pre-exposure prophylaxis (PrEP), if acute HIV is ruled out. HIV antibody appears after seroconversion, so conventional HIV antibody testing, even with a fourth-generation test, may be falsely negative during the acute seroconversion illness. The prevailing view that ART is indicated at any stage of HIV infection derives from a shifting landscape of risk and benefit. With better observational data, HIV has been shown to be associated morbidity and mortality due to diverse causes apart from AIDS-related complications. Further, ART agents have become more potent, less toxic, and less vulnerable to the development of drug resistance. See Table 5.1 for a list of drugs used to treat HIV infection.

Ongoing HIV replication in the presence of the selective pressure of ART can lead to resistance to the ART agents. The likelihood of the developing resistance to a given drug varies according to its "barrier to resistance." Drugs like NNRTIs and lamivudine/emtricitabine have a low barrier to resistance, so resistance is quite likely to emerge during when VL is not fully suppressed. By contrast, PIs and INSTI have a higher barrier to resistance. When the selective pressure of ART is removed, the drug-sensitive virus may come to dominate the viral population, but drug resistant virus may be present as a minority species (archived drug resistance) and can reemerge if the drug to which the virus is resistant is used again. A baseline drug resistance test can identify transmitted drug resistance in patients with newly diagnosed HIV. For ART-experienced patients, results of past resistance tests can demonstrate resistance that may emerge again. Genotypic drug resistance assays identify specific mutations in the viral genes which code for the HIV RT, PI, and integrase which are known to confer resistance. In a phenotypic assay, the relevant genes from the patient's HIV are introduced into a laboratory HIV strain and then introduced into cell cultures with and without ART drugs to assay the effect of the ART drugs in vitro on the patient's strain.

Table 5.1 HIV drugs

Drug class	Drug names	Mechanism of action	Complications/ interactions	Advantages	Dosing
NRTI, nucleoside analogue reverse transcriptase inhibitor	Lamivudine(3TC), emtricitabine, abacavir(ABC), tenofovir disoproxil fumarate(TDF), alafenamide (TAF)	Compete with nucleosides, terminating DNA formation	Abacavir causes systemic hypersensitivity reaction in patients with the HLA B5701 gene	TAF has less mitochondrial toxicity and less renal toxicity than TDF	Dual NRTI backbone: abacavir/lamivudine (ABC/3TC) 600 mg/300 mg—1 daily (Epzicom)—check HLA B5701 for ABC hypersensitivity reaction (HSR) TDF 300 mg/emtricitabine 200 mg (TDF DF/EMT)—once daily (Truvada) TAF la* 25 mg/emtricitabine 200 mg (TAF/EMT)—once daily (Descovy) *TAF is preferred over TDF—less renal/bone toxicity

PI, protease inhibitor	darunavir*(DRV)*, atazanavir*(ATZ)*, fosamprenavir, nelfinavir, indinavir	Blocks virion assembly	Hyperglycemia, hyperlipidemia	*DRV* is the drug of choice as it can be used in patients with PI resistance and requires fewer pills daily	*DRV* 800 mg, must use with booster ritonavir 100 mg RTV or coformulated with booster cobicistat (Prezcobix)—once daily, with food. *ATV,* unboosted 400 mg (2 × 200 mg caps) or boosted 300 mg with 100 mg ritonavir or coformulated with booster cobicistat as Evotaz—once daily, with food. Less hyperlipidemia. Asymptomatic unconjugated hyperbilirubinemia common. Renal stones. Must use boosted with *TDF, EFV*
PI booster	Ritonavir*(RTV)*, cobicistat	Blocks hepatic metabolism of PI	Hyperglycemia, hyperlipidemia	Permits once daily PI dosing	

(continued)

Table 5.1 (continued)

Drug class	Drug names	Mechanism of action	Complications/ interactions	Advantages	Dosing
NNRTI, non-nucleoside reverse transcriptase inhibitor	Nevirapine(*NVP*), efavirenz*(EFV)*, rilpivirine*(RPV)*, etravirine*(ETR)*	Inhibits reverse transcriptase enzyme	*NVP* should not be initiated if CD4 count is above 400/ mm^3 (women) and 250/mm^3 (men) due to risk for severe hypersensitivity. *EFV* is associated with neuropsychiatric side effects	*ETR* is tasteless and dissolvable for patients with swallowing difficulties	*EFV*—600 mg once daily. Transient neuropsychiatric side effects, teratogenic first trimester *NVP* 400 mg once daily—not started at higher CD4 counts-- in men CD4 > 400, women CD4 > 250 due to potential for HSR/Stevens-Johnson syndrome. *RPV* 25 mg—once daily, MUST be taken with food. Not recommended for HIV PCR > 100,000/mL. TINY tablet. (Edurant) *ETR*—200 mg BID or 400 mg q day, after a meal. Easily dissolves in water, tasteless

INSTI, integrase strand transfer inhibitors	raltegravir (*RAL)*(RAL), dolutegravir(*DTG)*, elvitegravir*(ELV)*, (bictegravir—anticipated approval)	Blocks incorporation into proviral DNA	Class with few side effects *DTG*, bictegravir is preferred due to less resistance *ELV* must be given with a booster	Well tolerated	*RAL* 400 mg twice daily *DTG* 50 mg once daily *ELV* 85 mg or 150 mg—Always given with booster

These pivotal studies are the basis for the recommendation to treat everyone, at all CD4 counts. Patients should appreciate the solid basis for treatment guidelines:

- SMART (2001–2006)—continuous ART is better than intermittent CD4-guided ART in patients with CD4 > 350/mm [10].
- START—ART initiation at CD4 > 500 is better than initiation at CD4 > 350/mm^3 [11].
- HPTN 052—ART reduced HIV transmission in serodiscordant couples [12].

With current ART, a progressive and fatal disease has become easily manageable. Those whose HIV infection is discovered in the latest stages can experience a return to health lasting decades with ART. Older patients, with newly discovered HIV infection, may fear ART due to knowledge of earlier more toxic and less effective therapy. The new generation of newly infected younger patients may have little awareness of deadly potential of untreated HIV and may fail to adhere to therapy, thereby jeopardizing their own health and further fueling the current epidemic.

Testing for HIV in the Primary Care Setting

Educate

Before offering HIV testing, common misconceptions should be explicitly addressed. Worldwide, the most common mode of HIV transmission is heterosexual sex. HIV can be transmitted unknowingly by healthy, asymptomatic individuals. The clinical latency between infection and illness is years to decades, so current sexual activity is not the only indicator of risk. An individual whose partner is HIV negative should not conclude that he/she must also be HIV negative. Also, HIV can be transmitted by unrecognized blood exposures—for example, tattoos, ritual practices, unregulated medical practices, etc. Individuals who do not perceive themselves as "pro-

miscuous" or drug using may erroneously assume that they are not at risk and may decline testing. Higher-risk individuals, like men who have sex with men and drug users as well as their partners, have ongoing risk and so should be tested at frequent intervals. Higher-risk individuals can be informed of the availability of PrEP to prevent HIV acquisition. Engaging high-risk individuals in medical care can reduce HIV risk both through PrEP and with STD screening and treatment, since STDs facilitate HIV transmission and acquisition.

Testing for HIV

Universal screening: HIV testing can be offered in the context of all routine age-appropriate screening. HIV screening has an excellent cost/risk to benefit ratio. HIV screening is mandatory for blood/organ donation, organ transplantation, and purchase of life insurance.

Pregnancy: All pregnant women are offered HIV testing. ART during pregnancy is safe and prevents mother-to-child HIV transmission during pregnancy and childbirth. Pregnancy is an indication for HIV treatment.

Newborns: All newborns are screened at birth for passively transmitted maternal HIV Ab. This is default mandatory screening of mothers.

High-risk groups, due to social, demographic, and behavioral attributes: Members of high-risk groups include men who have sex with men (MSM), transgender women, IDUs and ex IDUs, sex partners of persons in high-risk group, sex partners of a person with uncontrolled HIV, victims of sexual assault, and vulnerable individuals (homeless, cognitively impaired, incarcerated, refugee, hearing impaired, sexually abused). Risk is also conferred by unregulated tattooing, unregulated medical practices, and ritual practices involving blood.

Patients with medical conditions suggesting risk of HIV acquisition: Receipt of blood or blood product transfusion before routine HIV screening (1985 in the USA), hemodialysis, hepatitis C

(often associated with prior IDU, exposure to contaminated blood), any STD (syphilis, gonorrhea, chlamydia, herpes simplex, hepatitis B, trichomonas, and genital/anal warts), cervical dysplasia, and infections with pathogens transmitted by fecal oral route like ameba, giardia, salmonella, shigella, campylobacter, and hepatitis A.

Patients with medical conditions, symptoms, and signs that can be symptoms of HIV-related immunodeficiency but non-AIDS defining: Bacterial pneumonia, dermatomal zoster, chronic kidney disease with proteinuria, pulmonary/extrapulmonary TB, cervical dysplasia, HPV-related cancers (cervix, anus, mouth, throat), lymphoma, onychomycosis, seborrheic dermatitis, eczema, unprovoked ear or sinus infections, and stroke. Symptoms such as encephalopathy, dementia, chronic diarrhea, chronic cough, and chronic skin disorder. Signs such as lymphadenopathy, splenomegaly, weight loss, oral thrush, and skin rashes. Any patient with unusual infections or recurrent infections should be screened for immunodeficiency conditions, including HIV.

Patients with laboratory abnormalities suggestive of HIV: Anemia, leukopenia, thrombocytopenia, polyclonal gammopathy, and monocloncal gammopathy.

Test to Detect HIV [13]

Tests to diagnose and to confirm of HIV are listed below:

- *IgG—positive 6–12 weeks after infection, chronic HIV
- *IgM—positive 3 weeks after infection and then wanes
- *p24 antigen (Ag)—positive 11–14 days after infection and then wanes
- *Rapid test—detects IgG, IgM (OraQuick), chronic HIV
- *Fourth-generation assay—detects IgG + IgM + p24 Ag, chronic and early HIV
- *HIV PCR—first test positive after infection, test of choice in acute HIV infection

HIV testing in some locales requires informed consent.

Clinical Management

Evaluation of HIV Asymptomatic or Symptomatic HIV Seroconversion Illness or Following an OI

Obtain baseline CD4 count, HIV PCR, and HIV resistance test. Also, check CBC, chemistry, serology for HBV, HCV, syphilis, and STD screen (GC, chlamydia from urine (all), cervix (F), throat, rectum (MSM), and tuberculosis screen (PPD, QFT, targeted TB history)).

START ART—assure insurance coverage for ART.

CHOICE of ART—guidelines see www.aidsinfo.nih.gov and IAS-USA in JAMA 2016:316:191.

ART for ALL patients; any CD4. See Fig. 5.1 and Table 5.2.

For patient with unknown ART history, a boosted PI, INSTI and 2 NRTIs can be used pending RES testing.

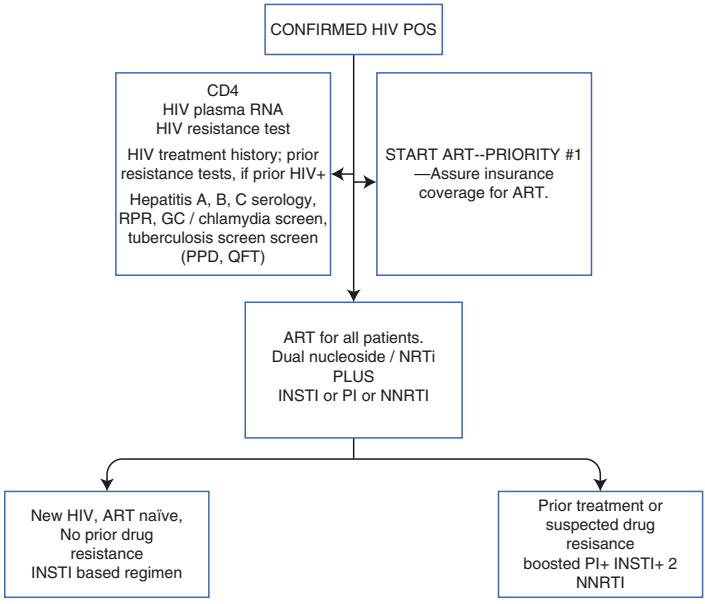

Fig. 5.1 Suggested starting regimens

Table 5.2 Preferred combined pill regimens

Initial preferred regimen	Single tablet regimens, without booster	Single tablet regimens, with booster
Descovy*(EMT/TAF)*/ Tivicay*(DTG)*—1 small pill each/once daily. No food issues. No booster, so fewer drug interactions	Atripla—*EFV/TDF/EMT*; big pill	Stribild—*ELV/cobi/TAF/EMT*
	Complera—*RPV/TDF/EMT*. Well tolerated. MUST take with food, for VL < 100,000/mL	Genvoya—same as Stribild, but with*TAF*
	Odefsey—same as Complera but with TAF instead of TDF. Well tolerated. MUST take with food. VL < 100,000/mL	
	Triumeq—*DTG/ABC/3TC*; BIG pill, no food restrictions. MUST check HLA B5701	

Rilpivirine and etravirine may be effective even if there is resistance to efavirenz and nevirapine.

Guidelines see www.aidsinfo.nih.gov and IAS-USA in JAMA 2016:316:191.

Care Recommendations at/near the First Visit

*CD-4 < 200/mm^3—screen for PCP, use PCP prophylaxis (trimethoprim sulfa 1 DS tab daily or every other

day)—can be stopped once CD4 > 100, with undetectable HIV PCR.

*CD 4 < 50/mm^3—screen for disseminated *Mycobacterium avium* complex disease (DMAC), wasting syndrome, and oral thrush (Table 5.3).

*FU HIV PCR after 2 weeks ART—expect one to two log drops in HIV PCR; expect undetectable HIV PCR by 6 weeks.

*Integrate age/risk/behavior specific health promoting interventions (see Table 5.3).

Evaluation of Symptomatic Patients with New HIV and CD-4 < 200/mm^3

Patients who are HIV tested due to symptoms must be evaluated to for the presence of an OI as the cause of the symptoms that prompted the HIV test. All patients should have CBC, chemistry, LDH, routine blood cultures, blood culture for *Mycobacterium avium* complex (MAC), serum cryptococcal antigen (CrAg), RPR, chest X-ray, relevant exposure history for TB, and endemic mycoses. See Table 5.4 for a description of OIs.

Timing of ART After an OI

ART started in the context of a recognized OI or in the presence of unexplained symptoms can lead to the paradoxical worsening of the OI or the unmasking of a previously occult OI. This is referred to immune reconstitution inflammatory syndrome (IRIS). ART, by improving immune competence, can cause a profound inflammatory response to an underlying OI, thereby paradoxically worsening symptoms. In general, OIs involving the CNS need to be treated longer prior to ART initiation since IRIS can be potentially catastrophic when it occurs in the confines of the brain or spinal cord. Further, OI s which cannot be speedily eliminated (TB, MAC,

Table 5.3 Ancillary interventions

Smoking cessation	HBV vaccine (all)[a], high dose	HAV vaccine (MSM, liver disease, other risks)[a]	Pneumococcal vaccine (all—Prevnar, followed by 23 valent Pneumovax)[a]	HPV (female and MSM < 26 years old)
Screen for latent tuberculosis with symptom screen, tuberculin skin test or interferon gamma release assay. If positive, obtain chest X-ray.	Regular STD screening—GC/chlamydia/syphilis common in MSM, treatable	Regular cervical cancer screening	Regular anal cytology[b]	

[a]For vaccines, can wait until CD4 rises >500/mm^3 or plateaus
[b]Plausibly beneficial

Table 5.4 Common opportunistic infections

Infection	Symptoms	Diagnostic test
Pneumocystis jirovecii pneumonia (PJP)	Fever, progressive exertional dyspnea (weeks), leading to hypoxia that worsens with exercise, dry cough without pleuritic pain	Chest XR shows typical diffuse interstitial infiltrates, without dense consolidation, effusions, or lymphadenopathy. LDH is elevated, WBC normal or low. Organisms can be seen in sputum or bronchoalveolar lavage fluid
Central nervous system (CNS) toxoplasmosis	Focal neurologic deficits that can be mistaken for stroke	Contrast-enhanced CT and MRI show characteristic multiple ring-enhancing abscesses. A positive serum toxoplasma titer is evidence of prior infection
Progressive multifocal leukoencephalopathy (PML)	Slowly progressive focal neurologic deficits which may be mistakenly attributed to "stroke"	JC PCR in CSF
Cryptococcus neoformans	Subtle and minimally localizing symptoms—headache, incoordination, with or without fever	Positive serum/CSF cryptococcal antigen or direct visualization of yeast by CSF microscopy

(continued)

Table 5.4 (continued)

Infection	Symptoms	Diagnostic test
Disseminated *Mycobacterium avium* complex (DMAC)	Fever, weakness, often with abdominal pain and diarrhea	Mycobacterial blood culture
Oral candidiasis	Cottage cheese-like plaque on the buccal mucosa and soft palate, difficulty swallowing solids more so than liquids	Resolution with antifungal treatment (fluconazole) Microscopic or pathologic exam of typical plaque
Tuberculosis (TB)	Productive cough, ascites, lymphadenopathy, fever	Culture of sputum, blood, bone marrow, or tissue biopsy (lymph node, liver, or other affected tissues)
Disseminated histoplasmosis	Pancytopenia, high LDH, fever, pulmonary infiltrates, abdominal pain, diarrhea, shock in patient with geographic risk[a]	Urine antigen or culture of sputum or blood
Coccidioidomycosis	Diffuse or localized pulmonary infiltrates, meningitis, lymphadenitis, or skin disease in patient with geographic risk[b]	Culture of sputum or blood Serology from blood or CSF

[a]Ohio River Valley, Caribbean, Central America, Africa
[b]Sonoran life zone—arid desert in Arizona, Nevada, California, Mexico border

Cryptococcus) or easily recognized (DMAC) prior to starting ART are the ones most commonly associated with IRIS.

PCP should be treated for a week before starting ART. CNS infections should be well controlled before starting ART. Patients with PML should start ART immediately. If they develop IRS, they should get steroids immediately. Patients who start ART in the presence of undiagnosed occult MAC may develop focal MAC IRIS after ART.

IRIS is usually managed symptomatically with anti-inflammatory medication (NSAIDS or steroids), continuation of ART, and antimicrobial agents appropriate to the OI.

Prevention of HIV

Safer sex using barrier protection—condoms, male and female.

Pre-exposure prophylaxis (PrEP)—for those at ongoing regular risk for HIV exposure who are unwilling to regularly use barrier precautions. The two-drug combination of TDF has been shown to reduce HIV acquisition in MSM—but only in those with detectable levels of drug in their blood. TDF is a particularly effective drug in MSM* since it concentrates in rectal mucosa. It is believed to be effective in women as well [10].

Post-exposure prophylaxis (PEP)—with 72 hours of known or suspected exposure to HIV using 30 day ART, usually INSTI plus Truvada (or according to drug resistance information if known from source case).

ART during pregnancy prevents vertical transmission from an HIV infected mother to child. Suppressive ART during pregnancy reduces transmission during pregnancy and childbirth. Where infant formula is available, breastfeeding is not recommended. Usual ART regimens are suitable for pregnancy.

Treatment of an HIV+ partner is prevention for HIV-negative partner in a serodiscordant couple.

Since young males who have sex with males (MSM) have reemerged as the dominant risk group for HIV acquisition in urban centers, education and prevention efforts targeted to this group are especially important.

Finally, a Bit of Humanity

For any patient with newly diagnosed HIV, irrespective of indication for testing, the initial encounter must address the patient's unspoken fears. Patients in the throes of a symptomatic OI may think that they are dying of AIDS. They can be reassured that most OIs are curable and that many years of good health can be reasonably expected. With current ART, the impact of HIV on physical well-being for most people is minimal.

The diagnosis of HIV can be emotionally devastating. Many people may fear stigma and ostracism. Women may fear that they cannot have children. Dating, sex, pregnancy, and intimacy are colored by HIV. Patients who themselves may have harbored negative views of HIV may now find those same stigmatizing attitudes among family and friends painfully personal.

The conversation about the unstated is usually the one that patients want to have. CD4, viral load, safe sex, condoms, and OIs may be a blur of irrelevance during that first encounter. The initial shock of an HIV diagnosis progressively wears off as the reality sets in of just how little life actually changes and just how asymptomatic HIV really is once ART is started. The process occurs over days, weeks, months, years, and, yes, decades. Talking about the distant future may help patients understand that HIV is a life sentence not a death sentence. Recognizing the fragility of life may actually be an epiphany.

For those concerned about death and longevity, we can honestly counsel that ART is very simple and very well tolerated and keeps people healthy for as long as we have been using it (decades). As far as sex, HIV is rarely transmitted by those who maintain an undetectable HIV VL, possibly even

without barrier protection. And for women, the fact that pregnancy is safe for mother and baby must be stated unequivocally. The fact that HIV is not transmitted by casual household contact (sharing food, living space, bathroom, etc.) needs to be communicated explicitly so patients are not afraid to care and be cared for by those close to them. This also serves to address sadly prevalent misconceptions among those who stigmatize HIV the most. Undocumented persons and others without insurance should be reassured, if appropriate, that programs exist which guarantee free care and medications. Young gay men need to have their specific concerns addressed. Concerns about privacy, disclosure, rejection, and safety, including the potential for intimate partner violence, should be sought and addressed. Patients need to emerge from that first encounter with optimism about their future. That optimism starts with a provider who is optimistic.

Clinical Pearls

- Maintain a high index of suspicion for HIV disease as it can masquerade as other illnesses.
- Compliance with medications is extraordinarily necessary for suppression of viral reproduction to elicit patients' concerns about the disease and its treatments.

Don' Miss This!

- Acute HIV infection can present like a cold or tonsillitis.
- Don't miss the chance to prevent infection in at-risk patients.

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Part II
Endocrine

Chapter 6
Diabetes

Ari Geliebter

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 a number of adverse short- and long-term consequences for 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]. 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

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_6

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 large increase in the global incidence of DM. According to the CDC, the number of Americans diagnosed with DM has increased fourfold between 1980 and 2014 [5]. As many as 29.1 million people, or 9.3% of the US population, have diabetes as of 2012, and nearly a third of those patients are unaware of their diagnosis [6]. Given the great benefit of tight glycemic control early on in the disease process, identification and screening high-risk individuals remains a priority.

The majority of patients fall into one of two categories: type 1 diabetes or type 2 diabetes.

- Type 1 diabetes (T1D): an autoimmune disease in which the insulin-producing beta cells are destroyed, leading to an insulin-deficient state. Overall, 5–10% of all diabetics have T1D [7]. 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 diabetics 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), and drug-induced DM.
- 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 [7]:

1. Fasting plasma glucose of ≥126 mg/dL (fasting for 8 h)
2. Hemoglobin A1c ≥ 6.5%
3. Classic symptoms of hyperglycemia + plasma glucose of ≥200 mg/dL
4. 2-h plasma glucose of ≥200 mg/dL after a 75-gram oral glucose load

Pre-DM is diagnosed with the following ADA criteria [7]:

1. Fasting plasma glucose of 100–125 mg/dL
2. Hemoglobin A1c 5.7–6.4%
3. 2-h plasma glucose of 140–199 g/dL after a 75-gram oral glucose load

A single abnormal 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 T2D. Similarly, while certain characteristics such as obesity and dyslipidemia are more common in T2D, they can be encountered in T1D 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, GAD-65, IA-2 and IA-2B, and ZnT8 can be used to help aid in the diagnosis [7]. 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 [8]:

- Adults aged 40–70 who are overweight or obese
- Non-overweight patients younger than 40 with a family history of DM, personal history of gestational DM or polycystic ovarian syndrome, and certain racial/ethnic groups such as African-Americans, American Indians or Alaskan Natives, Asian-Americans, Hispanics or Latinos, or Native Hawaiians or Pacific Islanders

The ADA recommends repeat testing of high-risk patients every 3 years or more frequently in patients with higher-risk features such as pre-DM [7].

Key H&P

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 coexisting 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 Diabetic Patient

- Annual eye exam
- Annual monofilament test or other test for detecting neuropathy
- Hemoglobin a1c every 3–6 months depending on control
- Annual fasting lipid panel
- Annual urine albumin-to-creatinine ratio
- Blood pressure at every visit
- Annual influenza vaccine and pneumococcal vaccine at appropriate intervals

Treatment

Effectively treating DM requires a patient-centered approach that includes lifestyle modification, glycemic control, and management of comorbid conditions such as obesity, hypertension, 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, intensive glycemic control has not been consistently found to reduce macrovascular complications in T2D, and therefore a more comprehensive cardiovascular risk

reduction strategy should be implemented addressing the traditional risk factors of hypertension, hyperlipidemia, smoking cessation, and weight loss.

Treatment Goals in DM [9]

6.0–6.5%: patients with new DM diagnosis lack of comorbidities, and if able to avoid adverse outcomes with therapy

7.0–8.0%: patients with long-standing DM, high risk for hypoglycemia, multiple comorbidities

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 a continuous subcutaneous insulin infusion ("insulin pump"). Prandial insulin should account for the anticipated carbohydrate intake and pre-meal sugars, and a personalized assessment for prandial insulin requirements is a essential 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) may be used to further assess glycemic management and has been associated with hemoglobin A1c reductions.

Type 2 Diabetes

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have published comprehensive treatment guidelines for T2D [1, 9]. While there are many different treatment approaches for patients with T2D, it is important that the chosen approach be mutually 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 [9]. 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 the majority of 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 a number of pathophysiological defects in T2D, and combination therapies that address several of these defects should be considered in all patients [10].

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.

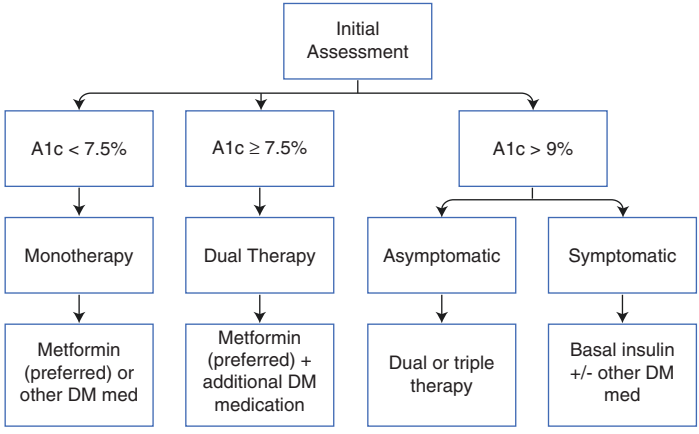

Fig. 6.1 Initial glycemic management (Adapted from the AACE Glycemic Control Algorithm, 2016)

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% (AACE guidelines) should be considered to reduce microvascular and macrovascular disease [9]. In adults with a longer diabetes course, 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. 6.1 for a suggested pharmacological approach to glycemic management.

Choice of Therapy

Both the American Diabetes Association and the American Association of Clinical Endocrinologists have created comprehensive algorithms for pharmacotherapy in T2D [1, 9]. Below is a summary of commonly available diabetic medications, also summarized in Table 6.1.

TABLE 6.1 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, 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		0.5–2 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, pancreatitis
Liraglutide		0.6–1.8 mg	Daily	
Dulaglutide		0.75–1.5 mg		

TABLE 6.1 (continued)

Drug name	Route	Dosage	Timing	Notable side effects
Dipeptidyl peptidase 4 (DPP-4) inhibitors [MOA: Inhibiting DPP-4, thereby increasing GLP-1]				
Sitagliptin	Oral	25–100 mg	Daily	Pancreatitis, rare hypersensitivity reactions
Saxagliptin		2.5–5 mg		
Linagliptin		5 mg		
Alogliptin		6.25–25 mg		
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, lower extremity amputations
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		

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.

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/min/1.73 m^2, should be reconsidered in patients already on metformin when eGFR drops below 45 mL/min/1.73 m^2, and should be stopped completely when eGFR drops below 30 mL/min/1.73 m^2. Metformin should also be stopped prior to imaging studies with iodinated contrast [11].

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, Albiglutide, Dulaglutide)

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. They may be used as add-on therapy to metformin and potentially as an alternative to basal insulin therapy in selected patients. GLP-1 receptor agonists are injectables and are available in twice-daily, daily, and weekly formulations. Liraglutide has demonstrated cardiovascular safety in high CV risk patients [12]. Exenatide should not be used with eGFR <30 mL/min.

Adverse Effects

Gastrointestinal side effects include nausea, vomiting, and diarrhea and may be improved 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, are dosed once daily, and are available in combination with metformin. 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. There have also been rare reports of hypersensitivity reactions.

SGLT-2 Inhibitors (Canagliflozin, Dapagliflozin, Empagliflozin)

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 also result in decreased blood pressure. Empagliflozin has been found to lower all-cause and cardiovascular death and to lower the risk of heart failure hospitalizations [13]. 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, as well as an association with bone fractures. Some reports have described the development of euglycemic ketoacidosis with SGLT-2 inhibitor use. There has been an increased incidence of leg and foot amputation with canagliflozin.

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 postprandial 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 is an effective treatment to lower blood glucose and may be the appropriate initial choice of therapy in certain clinical situations. Long-standing diabetics already on two

Table 6.2 Insulin formulations

	Onset	Peak effect	Duration
Insulin: long acting			
Degludec U-100/U-200	30–90 min	None	42 h
Detemir	1 h	None	12–24 h
Glargine U-100/U-300	1.5 h	5 h	24 h
Insulin: intermediate acting			
NPH	1–2 h	5 h	12–24 h
Insulin: rapid acting			
Regular U-100/U-500	½–1 h	2–4 h	6–8 h
Lispro/aspart/glulisine U-100/U-200	<15 min	1–2 h	4–6 h

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 may be useful to help rapidly lower the A1c and improve symptoms [9].

Insulin can be given as either a basal dose to help suppress hepatic glucose production or as a prandial dose to help improve postprandial spikes in glucose. See Table 6.2 for a listing of commonly used insulin formulation and peaks of onset. 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 blood glucose of <110 mg/dL. Some patients with significant insulin resistance may require very high doses of insulin in order to achieve their glycemic targets. If patients are unable to reach their target hemoglobin A1c with basal insulin, the addition of prandial insulin can be considered with the goal of a 2-h postprandial glucose of <140 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 US 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 40–70 years old and overweight.
- A target hemoglobin A1c of 6.0–6.5% should be considered in newly diagnosed diabetics without significant comorbidities.
- Given the many treatment options available in T2D, patients and providers should be in agreement about glycemic aims before a new regimen is initiated.
- Insulin therapy is eventually required in many patients with diabetes.

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 7
Lipids

Dan L. Li

Introduction

Hyperlipidemia, also called dyslipidemia, is defined as increased serum levels of lipids, including cholesterol and triglycerides. It might be secondary to other diseases, such as diabetes mellitus, HIV, nephrotic syndrome, hypothyroidism, and other metabolic disorders, or due to genetic causes in the case of familial hyperlipidemia, which is termed as primary hyperlipidemia [1].

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 an important task in primary care practice.

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_7

Key H&P

History

Lipid disorders usually are asymptomatic. The history is focused on the patient's other medical conditions, family history, lifestyle, and risks of cardiovascular disease.

Medical History

A review of the patient's medical history is critical to identify possible medical conditions that could potentially lead to hyperlipidemia and to evaluate 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. Specifically, early-onset cardiovascular disease in first-degree family members is an important risk factor for ASCVD and should also be ascertained.

Social History

The patient's dietary patterns, physical activities, 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]. 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.)

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 non-coronary 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].

A fasting test can 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 2013 ACC/AHA guidelines recommend calculating 10-year ASCVD risk and lifetime risk for patients younger than 65 using the ASCVD risk calculator [9, 10]. The calculator is based on the observation data from the Framingham Study and additional studies on predominantly White and African-American populations. Therefore, in evaluating patients of other racial backgrounds, the estimated risk might need to be adjusted.

The 2013 ACC/AHA guidelines recommend recalculation of 10-year ASCVD risk every 4–6 years in patients 40–75 years of age who do not have clinical CVD and adjust treatment strategies accordingly [9, 10].

Other high-risk features should also be considered while assessing a given patient's cardiovascular risk, including family history of premature CVD. Additional tests such as high-sensitivity C-reactive protein (hs-CRP), coronary artery calcium (CAC) score, and ankle-brachial index (ABI) can improve the prediction of ASCVD [11–14], especially when there is uncertainty with respect to initiating treatment according to ASCVD risk calculator alone.

Treatment

Based on randomized clinical trials, in 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) released updated guidelines for cholesterol management [9, 10]. Instead of targeting LDL-level goals, which was recommended by the previous Adult Treatment Panel (ATP) III guidelines [15], the ACC/AHA guidelines promote lipid-lowering strategies depending on the ASCVD risk [9, 10].

Patient Population to Treat

In the 2013 ACC/AHA guidelines, four groups have been identified that clearly benefit from statin therapy in prevention of ASCVD events: (1) patients with clinical atherosclerotic cardiovascular disease, (2) patients with LDL-c levels ≥190 mg/dL, (3) patients with type 1 or 2 diabetes with LDL-c levels ≥ 70 mg/dL, and (4) patients who have a calculated 10-year ASCVD risk ≥7.5% and an LDL-c level ≥ 70 mg/dL [7, 8].

Current evidence from randomized controlled trials fails to show benefit of statins for patients with (1) end-stage renal disease on hemodialysis, (2) heart failure (New York Heart Association Class II–IV), and (3) age ≥ 75 without clinical CVD. Therefore the current ACC/AHA guidelines do not have recommendations regarding treatment of hyperlipidemia for these three groups of patients [7, 8].

Goals of Treatment

In the 2013 ACC/AHA guidelines, the intensity of cholesterol management is dependent on a patient's 10-year ASCVD risk. For adult patients between 40 and 75 years of age with (1) clinical atherosclerotic cardiovascular disease, (2) LDL-c levels ≥190 mg/dL, (3) type 1 or 2 diabetes with LDL-c levels ≥70 mg/dL, and (4) a calculated 10-year ASCVD risk ≥7.5%, high-intensity statin therapy is recommended. For type 1 or 2 diabetic patients with LDL-c levels ≥70 mg/dL and a calculated 10-year ASCVD risk <7.5%, moderate-intensity statin therapy is recommended. For patients without the above features but who have a calculated 10-year ASCVD risk ≥7.5%, moderate- to high-intensity statin therapy is recommended [9] (Fig. 7.1).

In comparison, in 2016, the USPSTF updated its recommendations on lipid therapy, which differ from the 2013 ACC/AHA guidelines regarding statin therapy in primary prevention [16]. The USPSTF guidelines recommended low- to moderate-intensity statin therapy in patients between the ages of 40 and 75, without a history of CVD but who have at least one CVD risk factor (including diabetes) and a 10-year ASCVD risk ≥10% (B recommendation), and to consider statin therapy when the 10-year ASCVD risk is between 7.5 and 10% (C recommendation) [16]. The rationale for recommending less aggressive cholesterol management for patients without clinical ASCVD is that the absolute benefits were small given the low incidence of cardiovascular events in this population [17].

Since there is controversy on the timing of initiating treatment and the intensity of cholesterol management in patients without clinical CVD, other factors (e.g., family history, hs-CRP, CAC score, ABI, etc.) to aid in assessing the ASCVD risk will likely help guide clinical decisions in a patient with a borderline calculated ASCVD risk.

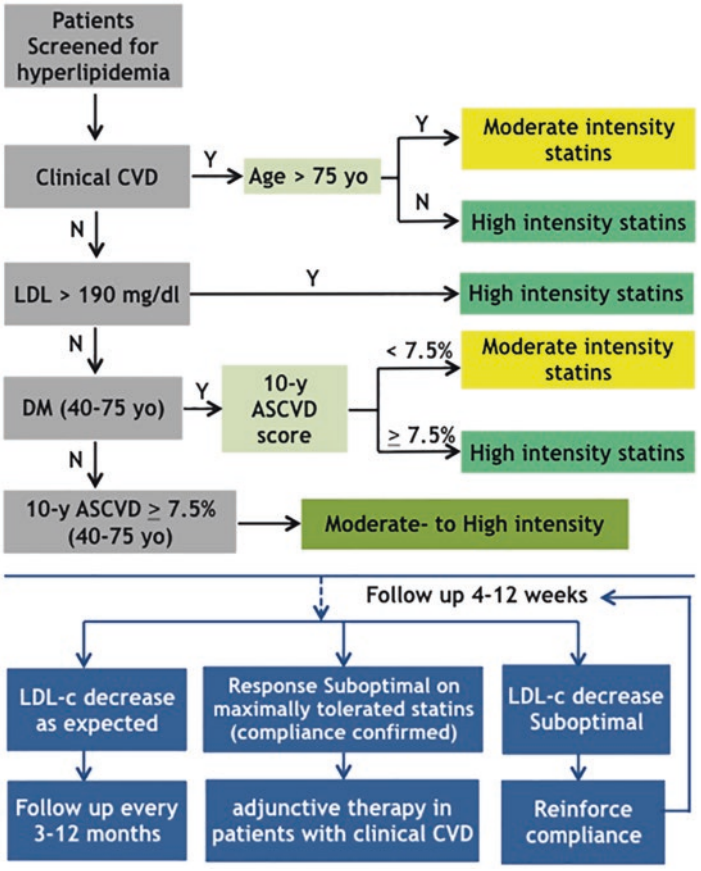

FIG. 7.1 Algorithm for cholesterol management recommended by the ACC/AHA guidelines

Treatment Strategies

Lifestyle Modification

Lifestyle modification remains a critical part of cholesterol management in the ACC/AHA guidelines. Lifestyle modifications include adhering to a healthy diet, regular

exercise, abstinence to tobacco products, and controlling body weight [18].

Certain dietary patterns (e.g., DASH diet, etc.) lower blood pressure and LDL-c [18]. The DASH diet is high in fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts. It is low in red meat, sweets, and sugar-sweetened beverages. The DASH diet has been shown to lower LDL-c by 11 mg/dL in adults with LDL-c levels <160 mg/dL (high strength of evidence) [18]. Further, reducing calories from saturated fat and trans fat has been shown to lower LDL-c [18]. The total calorie intake for a given individual is also critical.

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) [18]. The 2013 AHA/ACC lifestyle management guideline recommends engaging in aerobic physical activity (moderate to vigorous intensity, three to four sessions per week, and lasting 40 min per session) to lower LDL-c, non-HDL-c, and blood pressure [18].

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 and reduction of LDL-c [19] .

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 30–50% on average; and high-intensity statins achieve LDL-c reduction by more than 50% [9, 10]. Table 7.1 shows the various options of statins and dosages to achieve the targeted intensity of statin therapy.

Table 7.1 Suggested statin and dose for the appropriate intensity of therapy

Statin intensities		
High intensity (lower LDL-c > 50%)	Moderate intensity (lower LDL-c 30–50%)	Low intensity (lower LDL-c < 30%)
Atorvastatin 40 mg, 80 mg Rosuvastatin 20 mg, 40 mg	Atorvastatin 10 mg, 20 mg Rosuvastatin 5 mg, 10 mg Simvastatin 20 mg, 40 mg Pravastatin 40 mg, 80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2 mg, 4 mg	Simvastatin 10 mg Pravastatin 10 mg, 20 mg Lovastatin 20 mg Fluvastatin 20 mg, 40 mg Pitavastatin 1 mg

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% [20]. 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 [21]. 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 [22]. 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, 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 [22].

Statin therapy is associated with elevation of transaminase levels, which, however, is not indicative of liver injury in the absence of bilirubin level increase [23]. In many cases the elevations resolve with continuation of statin therapy. Significant liver injury is extremely uncommon with statin

use [23]. Routine tests of liver enzymes and liver function are not indicated following statin therapy [23].

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) [24], 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 have been used not uncommonly to treat dyslipidemia with elevated triglycerides. However, multiple studies to date failed to show efficacy in reducing cardiovascular events or all-cause mortality in type 2 diabetic patients [25–27]. While a subgroup analysis from a more recent study showed benefits of fenofibrate (RR 0.73, CI 0.56–0.95) in diabetic patients with triglycerides >204 mg/dL and HDL-c < 34 mg/dL, it also showed that fenofibrate increased myocardial infarction and stroke in female diabetic patients (RR 1.30, CI 1.01–1.68) [25].

Combination of Statins and Other Non-statin Medications

The 2016 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 [28]. The potential adjunctive therapy options include ezetimibe, bile acid sequestrants, and proprotein convertase subtilisin/kexin type 9 (PCSK 9) inhibitors. Niacin and fibrates, on the other hand, are no longer recommended [28].

Ezetimibe: Ezetimibe selectively inhibits cholesterol absorption by the small intestine. In combination with statins, ezetimibe has been shown [29] to produce an additional 23–24% reduction of LDL and further reduce ASCVD events in patients with clinical CVD.

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, resulting 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, there is no evidence for additive benefits of BAS as an adjunctive therapy to statins [28].

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 and thus reduces LDL-c level. Monoclonal antibodies to PCSK 9, evolocumab and alirocumab, as monotherapies or in combination with statins, have been shown to further lower LDL-c levels by 50–70% from baseline and reduce the risk of cardiovascular events [30, 31]. Both were approved by the US Food and Drug Administration (FDA) in 2015 to treat familial hypercholesterolemia and to achieve ASCVD secondary prevention as an adjunct to statins. Inclisiran, a long-acting RNA interference (RNAi) agent that inhibits PCSK 9 protein synthesis, has recently been tested in phase 1 trials, manifesting a robust and prolonged effect on LDL-c reduction as well [32]. While PCSK 9 inhibitors are exciting and powerful new agents for lowering LDL-c, their long-term efficacy and safety remain to be tested.

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, 10].

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 20–45 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.
- Fibrates effectively reduce the triglyceride level and, however, have failed to show cardiovascular benefits in multiple clinical trials.
- Four groups were identified to benefit from statin therapy: patients with clinical CVD, 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.

Don't Miss This!

SAMs can occur in about 10% of patients.

Be familiar with new effective drugs, including PCSK 9 inhibitors (and inclisiran, a long-acting RNA interference agent).

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Chapter 8
Thyroid Dysfunction

Nancy A. LaVine

Hypothyroidism

Introduction

Hypothyroidism (both overt and subclinical) is one of 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 119 million prescriptions in 2015 [3].

The hallmark of hypothyroidism is the insufficient production of thyroid hormones. This can be of a primary nature (underactivity 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 cases. In iodine-sufficient parts of the world, Hashimoto's autoimmune thyroiditis is the most common

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_8

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, extrapituitary tumors, inflammatory or infiltrative diseases)
- Drugs: amiodarone, lithium, interferon, methimazole, propylthiouracil, iodine, and iodinated contrast agents

Key H&P

The presentation of hypothyroidism can range from completely asymptomatic to floridly symptomatic. Symptoms may be influenced by the duration and severity of disease as well as the age of the patient and his or her 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 screening:

- Personal or family history of autoimmune thyroid disorders
- Autoimmune endocrine disorders (DM type 1, 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/Differential 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 an 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 an FT4 in the normal range – this is subclinical (or mild) hypothyroidism. The distinction between these categories has important implications for treatment.

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 [8]. The goal of treatment is to restore the euthyroid state and avoid such complications. 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 mcg/kg sufficient to reach a euthyroid state in most patients [9]. Alternatively, a dose of 25–50 mcg 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 mcg) and titrated up over several 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 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. Treatment of subclinical hypothyroidism with levothyroxine remains controversial. 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).

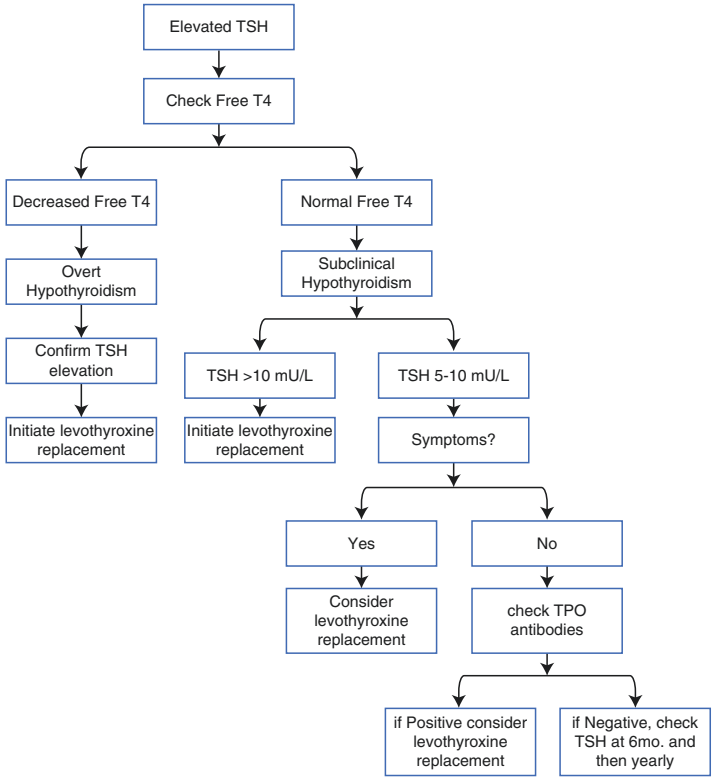

FIG. 8.1 Treatment algorithm for hypothyroidism

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, so 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.

Hyperthyroidism

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) [10] . 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 either T4 or T3. Subclinical hyperthyroidism is characterized by low serum TSH and normal levels of T3 and T4.

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

The most common etiologies for hyperthyroidism are listed below. Graves' disease, caused by autoantibodies stimulating the TSH receptor, is the most common etiology with 3% of women and 0.5% of men developing Graves' disease in their lifetime [11]. Other important etiologies include thyroiditis (subacute, silent, or postpartum), which leads to release of preformed thyroid hormone due to destruction of the thyroid follicles, and toxic nodular goiter, which is more common in iodine-deficient areas. The following algorithm outlines a strategy 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 generally 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 [12]. 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.

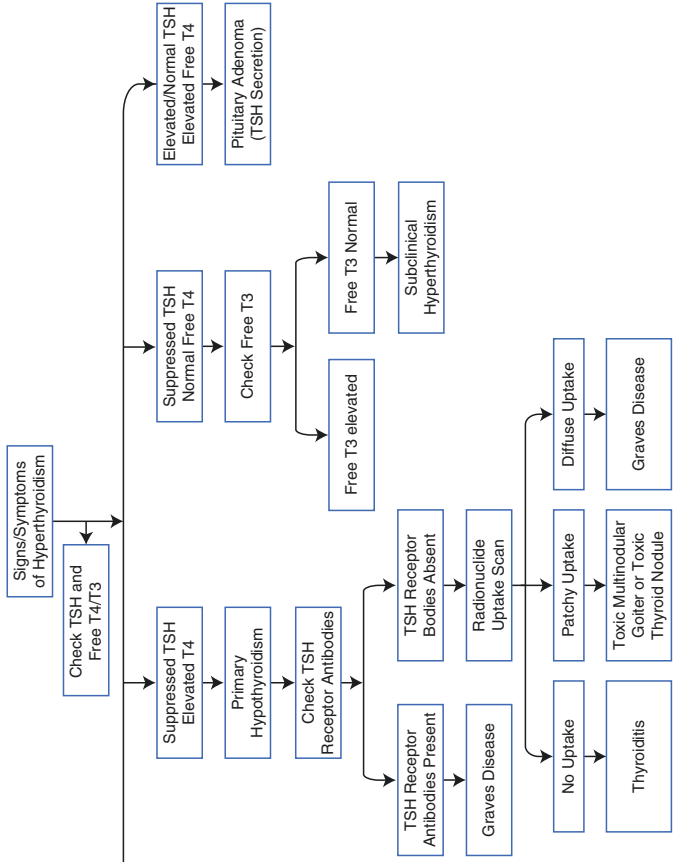

FIG. 8.2 Diagnostic algorithm for hyperthyroidism

Antithyroid drugs include methimazole and propylthiouracil (PTU). Use of these medications for 12–18 months results in remission in 40–50% of patients [13]. 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 to 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. 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 [14] 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 of patients on thyroid medications [15].

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 when free T4 levels drop below normal range.

Surgery

Indications for surgery include large goiters with compressive symptoms, suspicious thyroid nodules, and hyperparathyroidism [16].

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

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 [17], whereas ultrasound may detect nodules in 19–68% of a random population sample [18]. When evaluating thyroid nodules, it is important to exclude thyroid malignancy, which can occur in 7–15% of thyroid nodules [19].

Key H&P

Thyroid nodules are often asymptomatic. Important history to obtain 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 [17, 19]. 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 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 [19].

Clinical Pearls

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

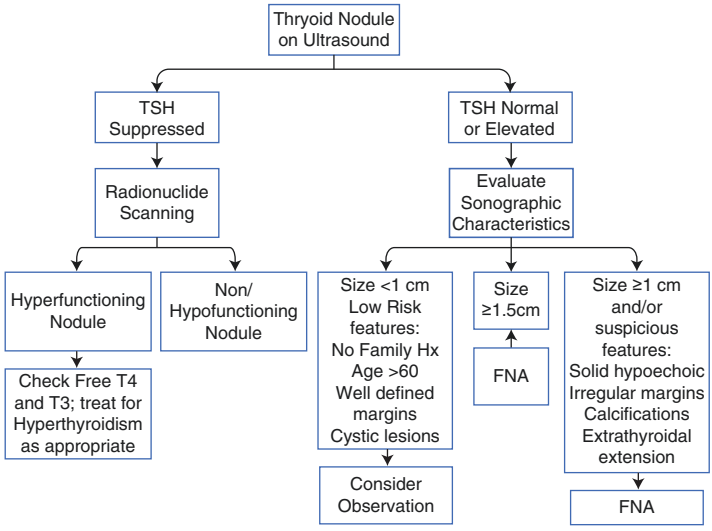

FIG. 8.3 Diagnostic algorithm for thyroid nodules

Don't Miss This!

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

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Chapter 9
Obesity

Gayotri Goswami and Jacinth S. Ruddock

Introduction

Obesity is a chronic, relapsing, multifactorial, neurobehavioral disease, wherein 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 more than 1 billion of the world's population are obese. This significant prevalence of obesity poses public health as well as economic concerns.

In 2014, 36.5% of the US population was considered to be obese [2]. Obesity is associated with an increased risk for developing many common chronic medical conditions. According to

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_9

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 [3]. An additional chronic medical condition was associated with 73% of these visits [3]. 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 [4]. The primary care provider is integral to getting patients engaged in the conversation about weight loss. However, primary care providers cite limited time, inadequate knowledge of obesity treatment, and lack of reimbursement as reasons obesity is not addressed [5].

This text hopes to aid in bridging the knowledge deficit. We provide a review of current 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 primary care provider about how weight loss may improve their health to be motivating, helpful, and appropriate [6]. As with most health issues, the conversation should be broached sensitively. 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 [7]. The terms fat, obese, and morbidly obese are most associated with stigmatization and blaming, while the terms overweight or unhealthy weight are more acceptable and motivating [8].

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 [7]. 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 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, sulfonylureas, insulin, atypical antipsychotics, 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 [7].

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 5As approach (Assess, Advise, Agree, Assist, Arrange) has been found to lead to improved weight-loss outcomes [9].

Physical Examination and Diagnostics

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.

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 [10]. 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 [7, 11]. 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 (Table 9.1).

Table 9.1 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

The measurement of neck circumference may be useful as part of calculating the STOP-BANG score as a screening tool for sleep apnea [12]. Please see the chapter on sleep apnea 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 [7, 11].

*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 weight-related complications (see Fig. 9.1). The Edmonton obesity staging system may offer clinical guidance in assessing obesity-related risk and prioritizing treatment [13] (see Table 9.2).

TABLE 9.2 Edmonton staging system [13]

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 in the interaction of genetic, environmental, and behavioral determinants. Adipose tissue becomes a dysfunctional endocrine organ leading to systemic metabolic disease [11]. 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 [14, 15].

Initial treatment includes lifestyle therapy which is the cornerstone of all weight-loss interventions (see Fig. 9.1). 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 [16, 17]. The three main components are:

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

Diet

To achieve weight loss, an energy deficit is required, and therefore reducing total energy (caloric) intake (500–750 kcal daily deficit) should be the main component of any weight-loss intervention. 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 [18–21]. 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 and requires medical supervision [11].

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 [22].

Physical Activity

The typical prescription included in a lifestyle intervention is as follows [11]:

- 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

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 ≥30 kg/m^2, without complications in whom lifestyle therapy fails to achieve weight-loss goals
- In individuals with a BMI ≥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 [23]. 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 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 FDA for the use in the treatment of obesity are orlistat (Xenical Alli): phentermine/topiramate extended release combination (Qsymia), lorcaserin (Belviq), naltrexone ER/bupropion ER (Contrave), and liraglutide 3 mg (Saxenda).

See chart 1 for specific information about each drug.

Weight-Loss Surgery

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 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 [24].

Surgical intervention is indicated for patients with:

- BMI of $\geq$40 kg/m^2 who have failed comprehensive lifestyle therapy and pharmacological means
- BMI of $\geq$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

Though evidence is limited, there may be benefit from surgical interventions for patients with diabetes or metabolic syndrome with a BMI of 30–34.9 kg/m^2 [11].

The procedures that are commonly used include:

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

See chart 2 for more information about common surgical options.

Long-term follow-up after uncomplicated bariatric surgery: Patents who have undergone bariatric surgery need lifelong follow-up visits. Follow-up with a multidisciplinary team consisting of the bariatric surgeon, nurses, registered dietician, 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 [25].

Clinical Pearls

1. Undesirable terms such as "heaviness," "fat," "large size," "excess fat," and "fatness" should be avoided when addressing issues regarding weight.
2. Lifestyle modification is the foundation of all treatment algorithms.
3. 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.
4. Obesity is a chronic disease and requires ongoing treatment. Patients will have varying motivation and adherence and will need ongoing encouragement.
5. 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.

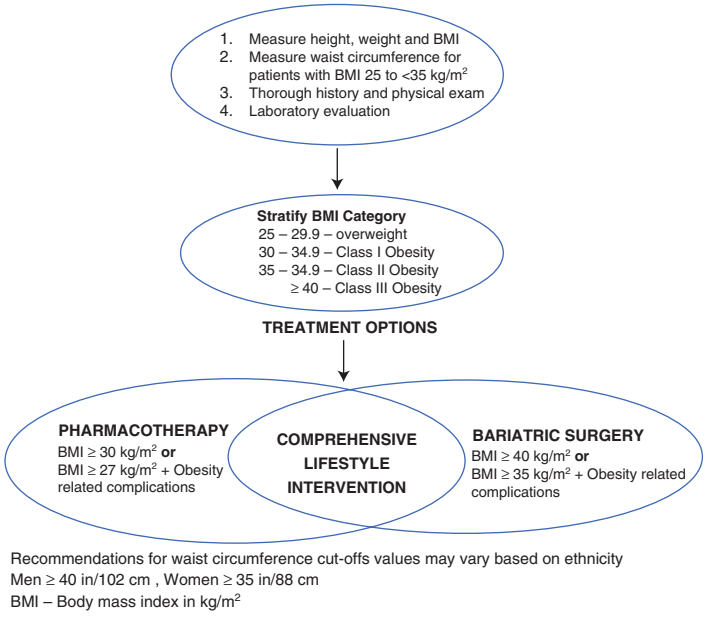

FIG. 9.1 Evaluation of a patient with increased weight

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 be sensitive and non-judgmental 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 9.3 and 9.4).

TABLE 9.3 Weight-loss medications: An overview

Medication (dosing)	Mechanism of action	% Total body weight loss	Side effects	Contraindications
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
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

Lorcaserin (*Belviq*) 10 mg PO BID	Decreases food intake and promote satiety by acting as a selective agonist to the serotonin 5HT2C receptors on the proopiomelanocortin neurons of the hypothalamus	1 year—3–3.6% 2 years—3.1%	Headache, nausea, dizziness, fatigue, xerostomia, dry eye, constipation, diarrhea, back pain, nasopharyngitis, hyperprolactinemia	Pregnancy and breastfeeding Creatinine clearance <30 History of depression
Naltrexone ER/bupropion ER (*Contrave*) Dose titration: Week 1: 1 table (8/90 mg) PO QAM Week 2: 1 table (8/90 mg) PO BID Week 3: 2 tabs (total 16/180 mg) QAM and 1 tab (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

TABLE 9.4 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

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Part III
Respiratory

Chapter 10
Cough

Israa Soghier and Kiyoshi Kinjo

Introduction

Cough is one of the most common presentations to both primary and secondary care providers. In most cases, the cause of cough can be identified with history, physical examination, and simple diagnostic tests. Sometimes chronic cough can be challenging to diagnose and treat and will require referral to a specialist.

Decision-Making/Differential Diagnosis

Cough can be divided into acute, subacute, and chronic based on the duration of the symptom. Acute cough exists for less than 3 weeks, while chronic cough persists more than 8 weeks [1]. Acute cough is most commonly caused by upper

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_10

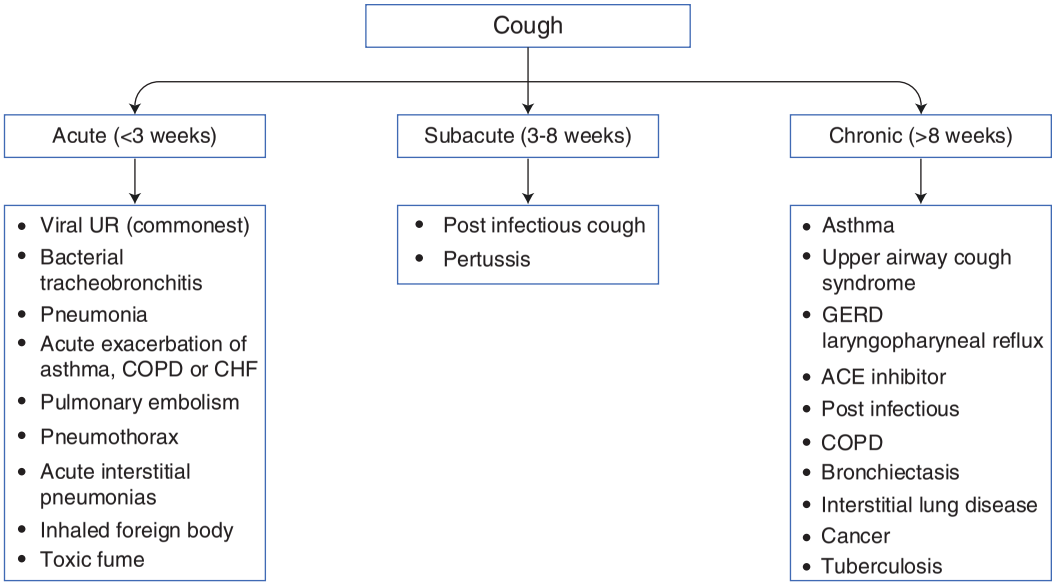

FIG. 10.1 Differential diagnosis of cough

respiratory infections. Other causes include pneumonia, bacterial tracheobronchitis, acute exacerbation of asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and pulmonary embolism (PE). It can also be an early presentation of chronic cough.

Subacute cough is most often due to postinfectious cough. *Bordetella pertussis* may play a significant role. Other etiologies overlap with chronic cough.

Chronic cough should be evaluated with a stepwise approach. After excluding the serious and obvious causes, diagnostic work-up should focus on asthma, gastroesophageal reflux disease (GERD), and rhinosinusitis (Fig. 10.1). More than one condition was found to be contributing to the persistence of chronic cough in up to 62% of patients [1].

Key History and Physical Exam

History taking should focus on the onset, duration of the cough, and presence of associated symptoms like postnasal drip, wheezing, dyspnea, and heartburn. One study suggested that the characteristics and timing of the cough are not usually helpful [2]. Significant sputum production points to an underlying pulmonary disease, e.g., bronchiectasis. Many patients report cough starting after an upper respiratory tract infection. Searching for triggers/aggravating factors including exposures, both at home and at work, tobacco use, and drugs may help identify the etiology. A history of past respiratory or heart disease should be elicited. A family history of cough can be seen in atopic patients and in those with an anatomic or neurological abnormality [3].

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 he/she looks relatively healthy, the likely diagnosis is upper respiratory infection.

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

Table 10.1 CURB-65 score

*C*onfusion
*U*rea >20 mg/dL
*R*espiratory rate >=30 breaths/min
*B*lood pressure (systolic <90 mmHg or diastolic =<60 mmHg)
Age >=65 years
1 point is assigned per criterion
0–1 points: risk of death <3%. Treat as outpatient
2 points: risk of death 9%. Consider hospitalization
≥3 points: risk of death 15–40%. Hospitalize and consider intensive care admission especially if 4 or 5 points

as pneumonia, acute respiratory distress syndrome, multi-organ 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 including asthma and COPD, renal failure, cancer, immunosuppressive conditions, e.g., HIV, and those receiving immunosuppressive drugs [4].

The most important differential diagnosis is pneumonia. 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 a dry cough. Bronchial breathing or crackles can be present 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 (Table 10.1) [5] or the pneumonia severity index (PSI) (Table 10.2) [6], to determine whether the patient can be treated as an outpatient or requires hospitalization [7]. The CURB-65 score is less well validated than the PSI but is easier to calculate [8]. Implementing the PSI results in fewer admissions without an

TABLE 10.2 Pneumonia severity index (PSI)

Sex
M (0 points)
F (−10 points)
Demographic factors
Age (1 point for each year)
Nursing home resident (10 points)
Comorbid illness
Neoplastic disease (30 points)
Chronic liver disease (20 points)
Heart failure (10 points)
Cerebrovascular disease (10 points)
Chronic renal disease (10 points)
Physical exam findings
Altered mental status (20 points)
Respiratory rate ≥30/min (20 points)
Systolic blood pressure <90 mmHg (20 points)
Temperature <35 °C (95 °F) or ≥40 °C (104 °F) (15 points)
Pulse ≥125/min (10 points)
Laboratory and radiographic findings
Arterial pH <7.35 (30 points)
Blood urea nitrogen ≥30 mg/dL (20 points)
Sodium <130 mEq/L (20 points)
Glucose ≥250 mg/dL (10 points)
Hematocrit <30% (10 points)
Partial pressure of arterial oxygen <60 mmHg or oxygen saturation <90% (10 points)

(continued)

Table 10.2 (continued)

Pleural effusion (10 points)				
Score	*Risk class*	*Risk*	*Mortality rate (%)*	
≤50 years + no points	I	Low	0.1	Outpatient
≤70	II	Low	0.6	
71–90	III	Low	0.9	Outpatient or short hospitalization
91–130	IV	Moderate	9.3	Hospital
≥130	V	High	27	

Table 10.3 Differentiation among asthma, COPD, and CHF exacerbation

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

increase in adverse events [9]. 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. Obtaining routine diagnostic tests to identify an etiologic diagnosis, e.g., blood and sputum culture, is optional for patients with community acquired pneumonia treated at home due to their low yield and small impact on clinical care [7].

Patients who are candidates for outpatient therapy and have no major comorbidities (chronic heart or lung disease,

diabetes, liver or renal disease, alcoholism, cancer, asplenia, or immunosuppression) and who have not taken antibiotics in the previous 3 months can be treated with macrolides or doxycycline. If there is a high incidence (>25%) of drug-resistant *Streptococcus pneumoniae* (DRSP) or if the patient has major comorbidities, a respiratory fluoroquinolone or a beta-lactam antibiotic (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime) plus either a macrolide or doxycycline is recommended [7]. The duration of treatment is a minimum of 5 days.

Acute exacerbation of asthma, COPD, or CHF is relatively easy to diagnose based on history, physical examination, and chest radiograph. All three can present with cough with dyspnea, orthopnea, and wheeze. Asthma tends to produce little sputum, while COPD exacerbation is associated with sputum (often purulent) and CHF with pink frothy sputum. Patients with asthma tend to get worse very early in the morning (Table 10.3).

The clinical presentation of PE is variable, but patients rarely present only with cough; patients also frequently complain of sudden onset dyspnea, pleuritic chest pain, hemoptysis, syncope, and symptoms of deep vein thrombosis (leg swelling and pain). 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.

Other etiologies of acute cough include pneumothorax (sudden onset chest pain, dyspnea), some types of interstitial pneumonia such as acute interstitial pneumonia and hypersensitivity pneumonitis (dry cough with dyspnea), and pleural effusion (chest pain and dyspnea). The history should also reveal the presence of a foreign body or inhalation injury.

The most frequent cause of subacute cough is postinfectious cough. Severity of cough is quite variable and can be disabling in some cases (e.g., sleep disturbance, stress incontinence, post-tussive vomiting). In most cases, the patient recalls a preceding episode of fever and upper respiratory symptoms. Some report persistent nasal symptoms indicating

postnasal drip as a mechanism of cough, while severe whooping paroxysmal cough spells might suggest pertussis. Pertussis can be diagnosed by nasopharyngeal culture, polymerase chain reaction (PCR), and serology. 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 helpful [10].

Chronic cough is more prevalent in middle-aged females. Women have more frequent cough than men and have heightened cough reflex sensitivity. Chronic cough should be approached systematically. In up to 93% of patients, an etiology can be found [11].

The first step is to rule out the serious causes and the most common ones by history, physical examination, chest X-ray, and spirometry. The presence of weight loss, fever, night sweats, chest pain, and hemoptysis suggests serious diseases including lung cancer and tuberculosis [3]. 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 15%) [12] usually producing little sputum. It usually 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 [13].

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 think it is from their smoking, so it is helpful to ask 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 obvious or serious causes are excluded, the three most frequent etiologies of chronic cough are (1) asthma, (2) GERD, and (3) rhinosinusitis [3, 14, 15]. These three 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 (Fig. 10.2).

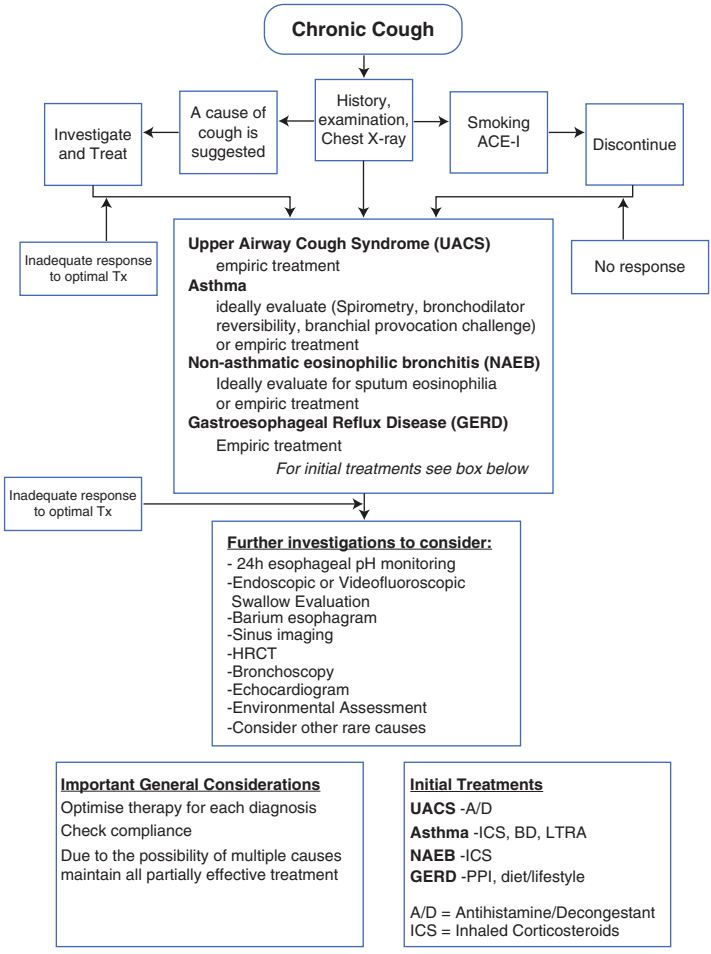

FIG. 10.2 Chronic cough algorithm for the management of patients ≥15 years of age with cough lasting >8 weeks. *ACE-I* ACE inhibitor, *BD* bronchodilator, *LTRA* leukotriene receptor antagonist, *PPI* proton pump inhibitor (Modified from Chest. 2006 Jan; 129(1 Suppl): 1S–23S. Irwin RS, Baumann MH, Bosler DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines)

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 (NO) may assist diagnosis. It is important to try to identify possible triggers/allergens and encourage avoidance. Empiric treatment with inhaled steroids can be tried. Some patients may require oral glucocorticoids for 1–2 weeks [16]. Non-asthmatic eosinophilic bronchitis is difficult to distinguish from asthma clinically. Sputum eosinophilia without bronchial hyperresponsiveness is diagnostic [3].

If the patient with chronic cough has GERD symptoms, proton pump inhibitors (PPI) should be given. Empiric trial with PPI for chronic cough in the absence of GERD symptoms is controversial, and the evidence is lacking [14]. Twenty-four hour esophageal pH monitoring correlates well with cough but does not predict a response to treatment [14]. It may be indicated in patients who have failed to respond to empiric treatment and when the diagnosis is in doubt.

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. Saline nasal irrigation can be tried.

Uncommon causes of chronic cough include sleep apnea, chronic aspiration, recurrent tonsillitis, external ear canal processes (e.g., earwax impaction), and psychogenic. When the diagnosis remains unclear, referral to specialists (pulmonary, otolaryngology, or gastroenterology) should be considered.

Treatment

Once the etiology is found, the specific treatment can be instituted. Acute cough is usually self-limited and requires only reassurance. Patients have reported relief from the use of over-the-counter medications, e.g., dextromethorphan, menthol, and first-generation antihistamines [3]. There is no role for antibiotics except in pertussis where macrolides may decrease the duration of cough if initiated within the first 2 weeks of symptoms [10]. When influenza is suspected, treatment with 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 serious complications and death [17].

As noted above, patients with chronic cough are treated empirically in many cases, but the evidence is weak, and the response rates are not perfect, creating frustration for both clinicians and patients. Symptomatic relief by antitussive medications is often suboptimal.

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 patient presents with chronic cough and no other obvious symptoms, asthma, GERD, and rhinosinusitis should be considered.

Don't 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 rhinosinusitis.
- Weight loss, fever, night sweats, and hemoptysis suggest a serious disease like tuberculosis or cancer. Order a chest X-ray/CT and sputum for acid-fast bacilli.

- Unilateral wheezing suggests an endobronchial lesion, e.g., cancer or foreign body. Order a chest CT and refer to a pulmonologist for bronchoscopy.

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Chapter 11
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. 11.1).

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_11

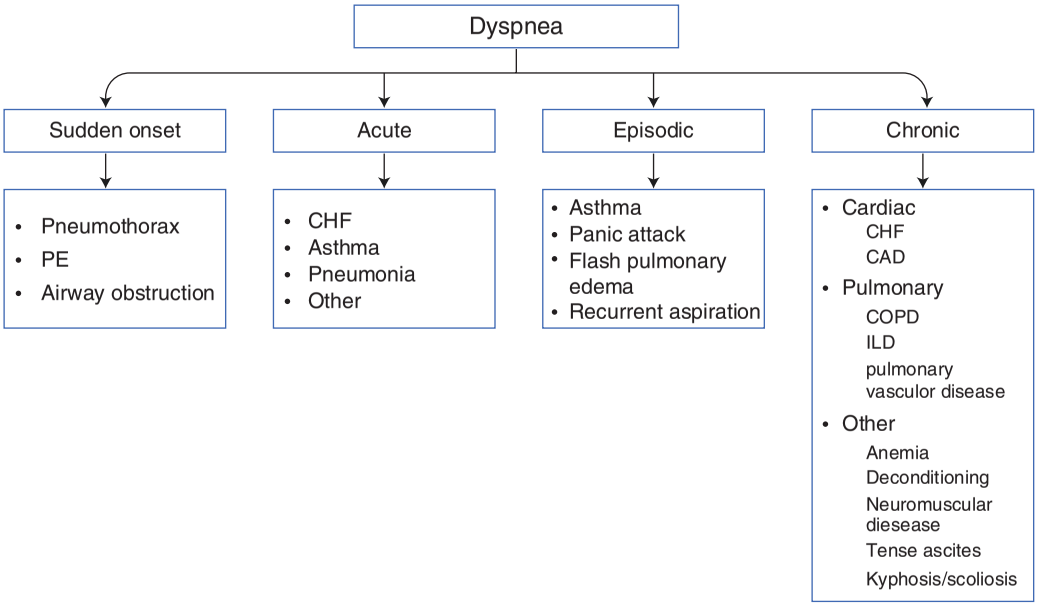

FIG. 11.1 Differential diagnosis of dyspnea. *PE* pulmonary embolism, *CHF* congestive heart failure, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *ILD* interstitial lung disease

Table 11.1 Wells prediction rule (simplified score)

Clinical characteristic	Score
Previous PE or DVT (deep vein thrombosis)	1
Heart rate >100 beats/min	1
Recent surgery or immobilization	1
Clinical signs of DVT	1
Alternative diagnosis less likely than PE	1
Hemoptysis	1
Cancer	1

Pretest probability
≤1: PE unlikely (low)
>1: PE likely (high)
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

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 11.1) should be used [3]. When the patient with suspected 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 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 (contract CT scan or VQ scan). If the transfer and imaging studies take time, empirical anticoagulation therapy in the absence of contraindication should be considered.

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 the 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) may be helpful to confirm the diagnosis.

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 non-cardiac 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.

TABLE 11.2 Common causes of chronic dyspnea

Diagnosis	History	Physical exam	Diagnostic test
CHF	h/o 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 y.o. 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 Work up underlying cause of anemia
Obesity/deconditioning	Dyspnea on exertion, sedentary lifestyle, obesity	Normal or obese	Exclude other etiologies

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 11.2).

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 11.3 [9]. In most cases, low-dose steroid inhaler is the preferred controller medication. Those who have infrequent asthma symptoms (less than twice a month, no night symptoms in 1 month, and no exacerbation in 1 year) can be treated only with a short-acting beta-agonist inhaler as needed. 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

TABLE 11.3 Stepwise asthma management

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller	None	Low-dose ICS	Low-dose ICS/ LABA	Medium/high ICS/ LABA	Refer to asthma specialist
Other controller choice	Consider low-dose ICS	LTRA Low-dose theophylline	Medium-dose ICS Low-dose ICS + LTRA	Add tiotropium High-dose ICS + LTRA	Add low-dose oral steroid
Reliever	As needed SABA		As needed SABA or low-dose ICS/formoterol		

ICS inhaled corticosteroid, *LABA* long-acting beta2-agonist, *LTRA* leukotriene receptor antagonist
Modified from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016

TABLE 11.4 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 + LABA ⇒If further exacerbation, LAMA + LABA + ICS ⇒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

1. Smoking cessation
2. Assess the symptom severity and exacerbation history and select bronchodilator treatment (see table above)
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 and pneumococcus

mMRC modified MRC dyspnea scale, *CAT* COPD assessment test, *LABA* long-acting beta-agonist, *SABA* short-acting beta-agonist, *LAMA* long-acting antimuscarinic antagonist, *SAMA* short-acting antimuscarinics, *ICS* inhaled corticosteroid

Global Initiative for Chronic Obstructive Lung Disease Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2017 Report)

inhaler and a long-acting beta-agonist (LABA). 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., sinusitis 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 11.4 [10]. FEV1 value is important to establish the diagnosis of COPD (post bronchodilator FEV1/FVC <70%), but the medication choice is strongly influenced by the degree of symptoms and the history of exacerbation. LAMA (long-acting antimuscarnic antagonists) 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. None of the pharmacologic therapies are shown to slow the decline of the lung functions; smoking cessation is the only definitive treatment of COPD. 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. Newer therapies including pulmonary rehabilitation and lung reduction surgery may be appropriate to consider. Comorbid conditions such as cardiovascular disease are very common in patients with COPD; screening and treatment of comorbidity is important.

Management of heart failure is summarized in Fig. 11.2 [11]. 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 [12].

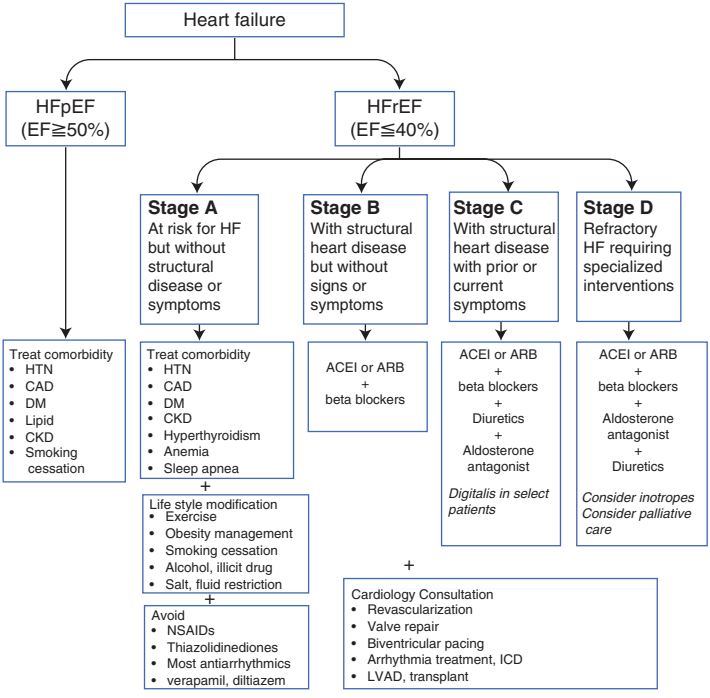

FIG. 11.2 Heart failure management. **Stage A**: Patients at high risk for heart failure but without structural disease or symptoms. **Stage B**: Patients with structural heart disease but without signs or symptoms. **Stage C**: Patients with structural heart disease with prior or current symptoms. **Stage 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. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Modified from Yancy CW, Jessup M, Bozkurt B et al. Circulation 2013; 128: 1810–52

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 quite ill.
- 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 12
Sinusitis

Shuchita Khasnavis

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 cases are viral in origin and only a small percentage are bacterial. The majority of cases resolve with conservative treatment [2]. 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 cheekbones
- Ethmoid sinuses: behind the nasal passages
- Sphenoid sinuses: near the optic nerve and part of the orbits

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

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_12

sinusitis include thick nasal discharge, facial pain or pressure, fever, and reduced sense of smell. 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 *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella*, *Staph. aureus*, and 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 occurs 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, and 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 septums 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:

- 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.

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].

Physical Findings

A patient with sinusitis usually presents with erythema, edema, or tenderness over the involved sinus [9].

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 [10]. Differentiation from common viral upper respiratory tract infection is important where nasal congestion is predominant without head congestion and facial pains. Presence of purulent secretions has the highest positive predictive value for clinically diagnosing sinusitis (Fig. 12.1).

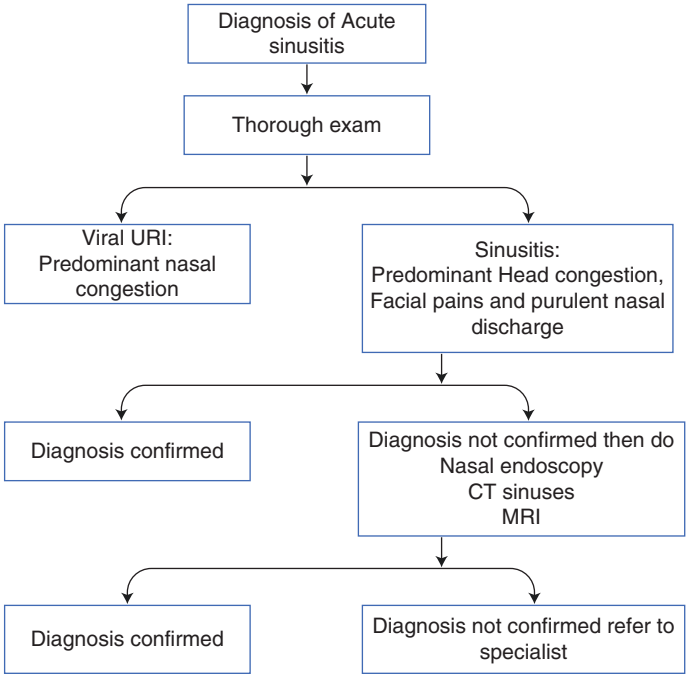

FIG. 12.1 Diagnostic algorithm for acute sinusitis

Diagnostic Tests

- *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 the 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 [10, 11].

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 duration of 7–10 days, high fever (>102), purulent nasal discharge, and worsening of symptoms after conservative management. Choice of antibiotics should cover the following: *S. pneumonia*, *H. influenzae*, and *M. catarrhalis* [11, 12].

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 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

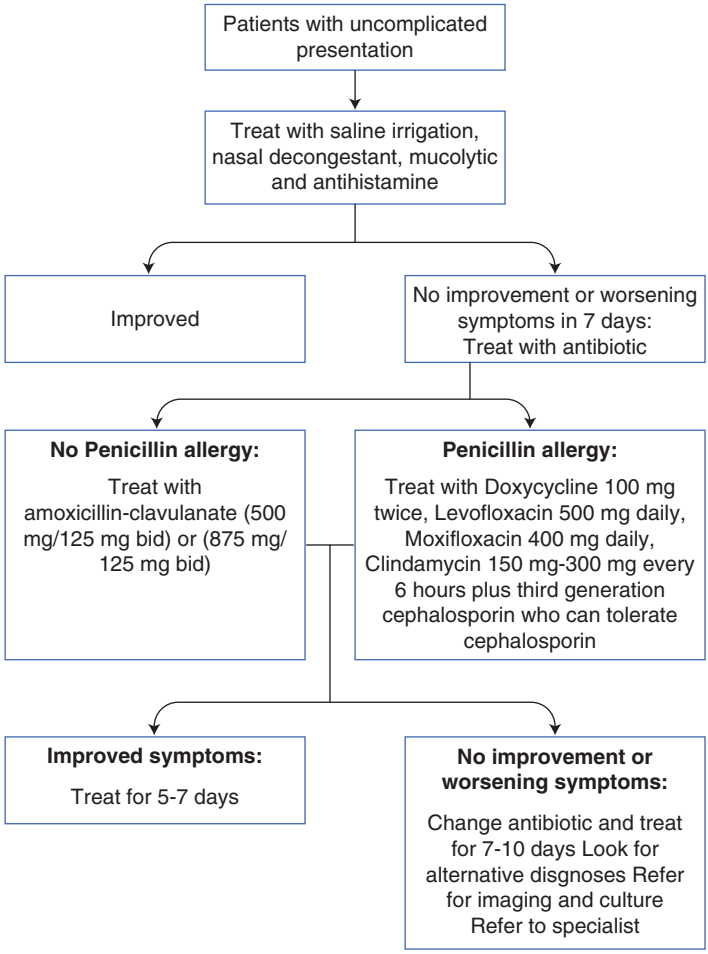

FIG. 12.2 Treatment algorithm for acute sinusitis

agent will depend on initial therapy), refer patients for imaging studies and send cultures, and consider alternative diagnoses (Fig. 12.2).

Risk Factors for Resistance to Antibiotics

Age > 65
Hospitalization in 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

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. Topical corticosteroids are not indicated for acute sinusitis.

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, 11]. Antibiotics should be continued for 4–6 weeks and should cover organisms causing acute sinusitis and also *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 [13]

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

Don't Miss This!

- 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 13
Sore Throat

Lori Ciuffo

Introduction

Although the most common cause of pharyngitis is viral, Group A streptococcal (GAS) pharyngitis is a significant cause of community infections [1]. A majority of patients with pharyngitis receive presumptive antibiotic therapy. One report estimates about 60% of adults seen in the USA in 2010 for a complaint of sore throat received an antibiotic prescription [2]. Group A streptococcus typically presents with abrupt onset of symptoms including sore throat, fever, and anterior neck pain related to lymphadenopathy. These symptoms may occur in association with headache or malaise. Late winter and early spring are peak GAS seasons. The infection is transmitted via respiratory secretions, and the incubation period is 2–4 days. The goal of therapy is to reduce complications including acute rheumatic fever and glomerulonephritis [3, 4]. Many patients with viral pharyngitis also have signs and symptoms associated with a viral upper respiratory infection including nasal congestion, coryza, hoarseness, sinus discomfort, ear pain, or cough. Coinfections with streptococci and viruses may occur [2].

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_13

Decision-Making/Differential Diagnosis

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. 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 [5, 6]. 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* [1]. Noninfectious causes include seasonal or environmental allergies, smoking or secondhand smoking, poorly humidified air, and gastroesophageal reflux disease (GERD) [3].

Key History and Physical Exam

The goal of the evaluation of adults with acute pharyngitis is to exclude potentially dangerous causes, to identify treatable causes, and to prevent complications including acute rheumatic fever. History of exposure to strep pharyngitis with exam findings including pharyngeal erythema, fever, tonsillar exudates with hypertrophy, 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 rash should be noted. The appearance of a whitish exudate in the mouth and pharynx (thrush) suggests fungal infection, seen in immunocompromised patients. Viral symptoms may include conjunctivitis, coryza, cough, diarrhea, coarseness, ulcerative stomatitis, or viral exanthem. Patients who present with unusually severe signs and symptoms,

including secretions, drooling, dysphonia, muffled voice, or neck swelling particularly if they have difficulty swallowing, should be evaluated for rare but serious throat infections/local abscesses [2, 4–6]. College-aged patients should be asked about sexual practices and risks, as they have an increased incidence of oral chlamydia and gonorrhea infections.

Diagnosis of Bacterial Pharyngitis

The modified Centor score (also known as McIsaac score) is a validated decision-making instrument that utilizes patient age and four specific signs and symptoms to determine the likelihood of having GAS [1, 7].

Modified Centor score [7]

Absence of cough	1
Swollen tender anterior cervical nodes	1
Temperature more than 100.4 °F	1
Tonsillar exudates or swelling	1
3–14 years	1
15–44 years	0
45 years or older	−1
Total score	*Testing and treatment recommendation*
Score = 0	No further testing or antibiotic needed
Score = 1	No further testing or antibiotic needed
Score = 2	Consider strep testing/culture
Score = 3	Consider strep testing/culture
Score = 4, 5	No further testing. Start antibiotic

The likelihood of GAS increases with the score; however, the score is equally useful for identifying patients for whom neither microbiologic tests nor antimicrobial therapy are necessary. Patients with a score of 1 or less are unlikely to have GAS and should not undergo further RADT testing or receive antibiotic treatment. Patients with a score of 4 or more should not be tested and antibiotics should be started. Patients with scores of 2 or 3 should receive RADT and, if indicated based on test results, given antibiotics. Other factors linked to increased likelihood of GAS infection are recent contact with a person with documented streptococcal infection and residence in a dormitory or group home.

Throat culture has been considered the gold standard to establish the microbial cause of acute pharyngitis. However, compared with RADT, culture results are not available for 24–48 and can cause a delay in diagnosis. Throat culture is primarily used as a backup test in patients with negative RADT where clinical concern for GAS or bacterial pharyngitis is high [1, 7].

Rapid antigen detection testing is 70–90% sensitive and 90–100% specific. The use of antibiotics should usually be based on RADT results. Since the RADT is not 100% sensitive, if there is such a high level of suspicion of GAS infection, warranting empiric antibiotic treatment and then testing are not economically sensible.

Throat culture is 90–95% sensitive and 95–99% specific. For patients with a modified Centor score of 1, but who are high risk (e.g., poorly controlled diabetics, immunocompromised patients, chronic steroid users, patients with a history of rheumatic fever, childcare workers, and the elderly), consider doing throat culture or RADT.

Culture results should guide therapy [1, 3].

See Fig. 13.1 for the modified Centor decision tree.

Treatment

Antimicrobial therapy is warranted for patients with symptomatic pharyngitis with GAS confirmed by RADT or culture. Antibiotics may also be used to mitigate the clinical course of pharyngitis due to Group C and Group G strepto-

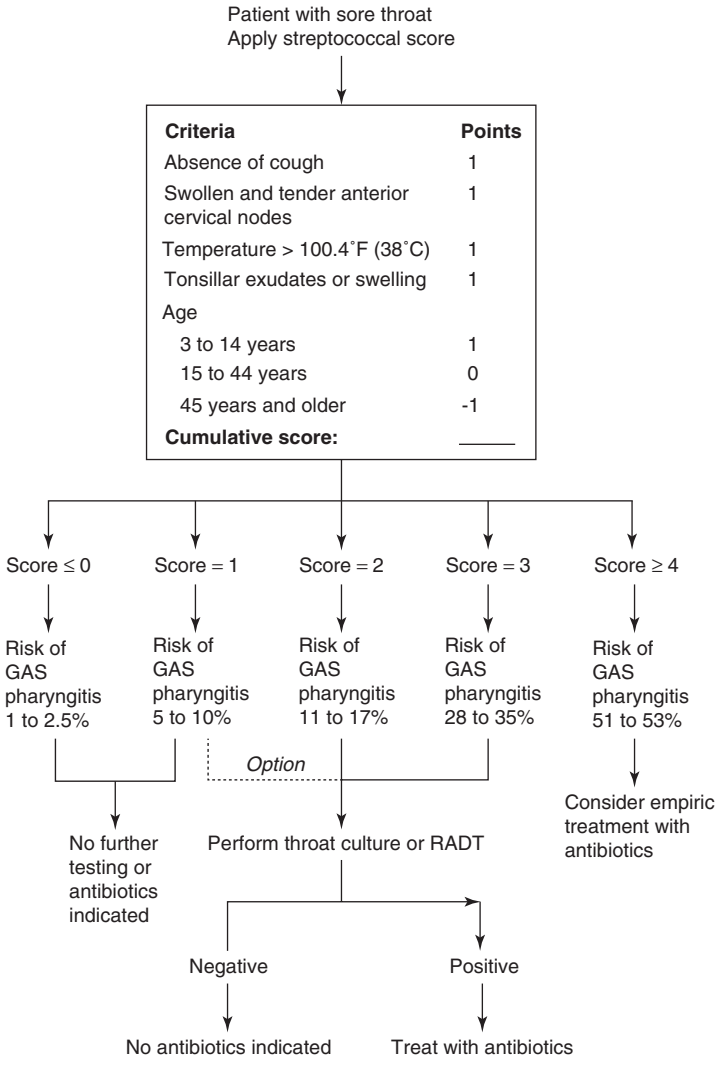

FIG. 13.1 Modified Centor score and management options using clinical decision rule. Other factors should be considered (e.g., a score of 1, but recent family contact with documented streptococcal infection). *GAS* Group A beta-hemolytic streptococcus, *RADT* rapid antigen detection testing. Adapted from McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ. 1998;158(1):79 [11]

cocci. However, treatment need not continue for 10 days since acute rheumatic fever is not a complication due to these organisms; therefore, treatment for 5 days is sufficient.

Oral antibiotic options for GAS pharyngitis include either a 10-day course of penicillin 500 mg twice a day, amoxicillin 500 mg twice a day, cephalexin 500 mg twice a day, clarithromycin 250 mg twice a day, clindamycin 300 mg three times a day, or a 5-day course of azithromycin 500 mg day 1 followed by 250 mg days 2–5. Intramuscular penicillin G benzathine (1,200,000 U single dose) may be administered to patients who cannot complete a course of oral therapy or to patients at enhanced risk for rheumatic fever or when compliance with therapy is in question. Sulfonamides, fluoroquinolones, and tetracyclines should not be used for treatment of GAS due to high rates of resistance and failure to eradicate the organisms from the pharynx. Patients with GAS pharyngitis generally improve within 3–4 days and are no longer contagious after 24 h of antibiotics [4, 8–10]. Carriers of GAS do not require antimicrobial therapy because they are unlikely to spread GAS pharyngitis to close contacts and are at little to no risk for developing complications.

Supportive therapy, such as an analgesic/antipyretic, is useful in most cases of sore throat, regardless of etiology [3].

Clinical Pearls

- Use the modified Centor score to guide testing and treatment of GAS.
- If there is high suspicion of GAS, start empiric treatment.
- The goal of treatment is to prevent complications and transmission. Treatment does not significantly shorten the duration of symptoms.

Don't Miss This!

- Evaluate for serious complications (abscess/local space infection) in patients presenting with sore throat and any of the following concerning symptoms: secretions, drooling, dysphonia, muffled voice, or neck swelling.
- Consider underlying immunodeficiencies in patients presenting with thrush.

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Chapter 14
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. Around 7–19% of adults in the USA reported not getting enough sleep, 40% report falling asleep unintentionally, and 50–70 million Americans have chronic sleep disorders [1]. Based on 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 [2].

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_14

ICSD3 Classifies Sleep Disorders into Seven Major Categories [2]

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 [3].

Sleep History

In addition to general medical, surgical, family, caffeine intake, 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 [4, 5].

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. doi: 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 [6], 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 [7].

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 [8]. 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. Hypopnea is defined by the decrease in airflow by 30–50%, associated with at least 3% oxygen desaturation,

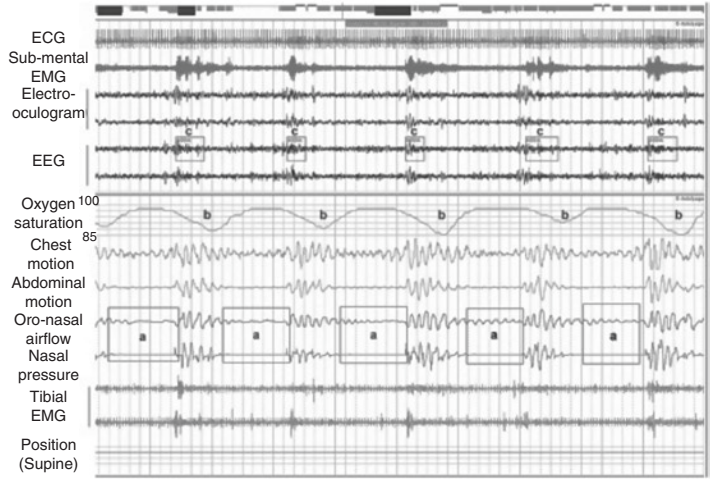

FIG. 14.1 Five-minute epoch of supine stage II sleep in a subject with severe OSA. Cessation (apnea) in breathing (**a**) result in arterial oxygen desaturation (**b**) and EEG arousal from sleep (**c**). Chest wall motion continues during the apneas indication that the events are due to upper airway obstruction [25]

followed by an arousal. AHI is the sum of apneas and hypopneas per hour of sleep. Respiratory disturbance index (RDI) is also used interchangeably with AHI (Fig. 14.1).

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 [9].

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.

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. 14.2).

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.

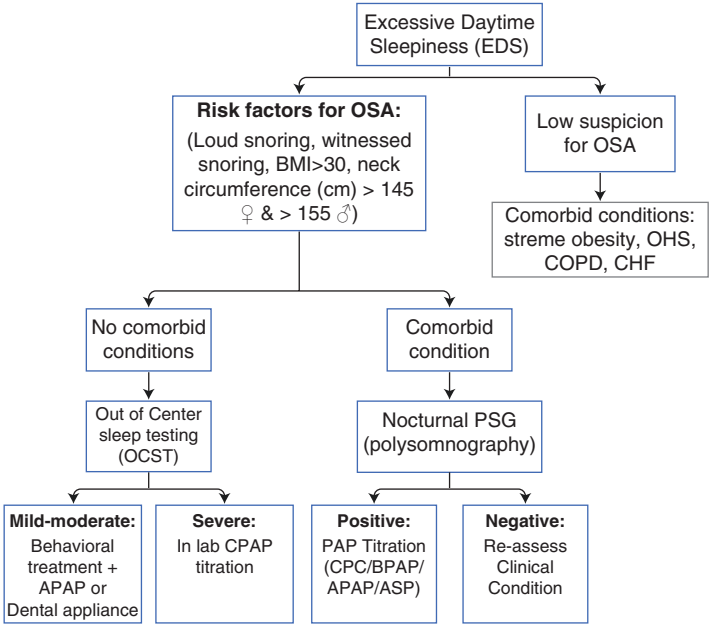

FIG. 14.2 Evaluation of excessive daytime sleepiness

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 [10, 11]. Recent data, however, states that there is significant decrease in morbidity, rather than mortality [4]; 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 [12]
- Surgery (effective for mild OSA): Uvuloplasty when if indicated is effective for primary snoring with or without mild OSA [13]
- UPPP (uvulopharyngopalatoplasty) and MMA (maxillomandibular advancement)
- Laser-assisted uvuloplasty (LAUP) and radiofrequency ablation
- Hypoglossal nerve stimulation (moderate to severe OSA) [14]
- Hyoid surgery: Hyothyroidopexy and hyoid myotomy with suspension
- Dental appliances (oral appliance therapy)

The most effective treatment and first-line therapy is continuous positive airway pressure (CPAP) [12]. 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 [15].

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 [16].

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 [14].

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 [17]. 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 [18].

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:

- 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 [19].

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. 14.3).

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).

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

(continued)

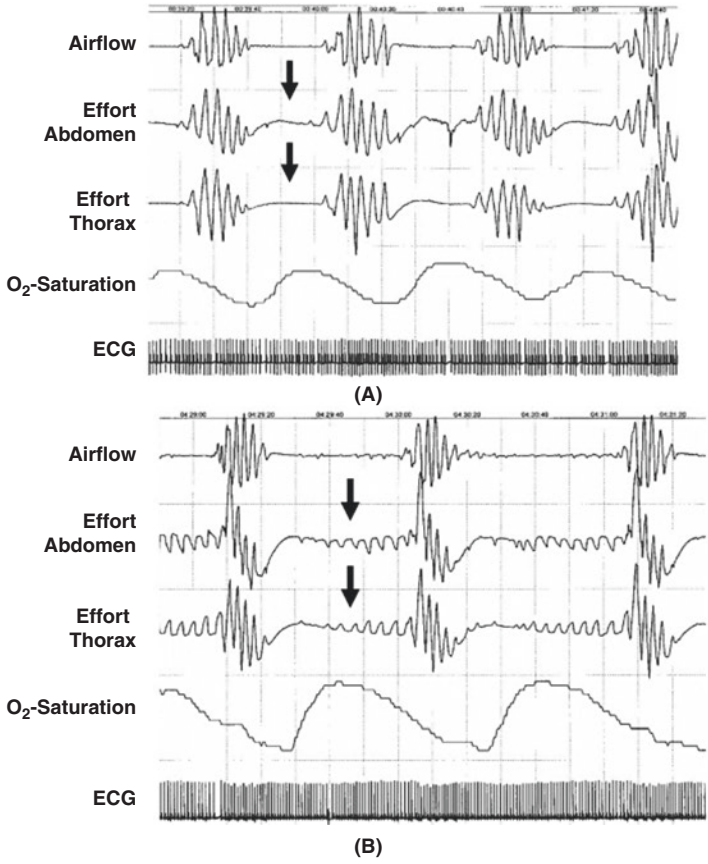

FIG. 14.3 Polysomnography (3 min) with central sleep apnea (**a**) and obstructive sleep apnea (**b**). Note the absence of chest efforts and abdominal movements in the absence of oronasal airflow in central sleep apnea but not in obstructive sleep apnea (*arrows*). Also, note the pronounced decrease in O2 saturation following each apnea episode [26]

(continued)

- 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 [20].

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 [21].

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 [22].

Circadian rhythm sleep-wake disorder: This group includes delayed sleep phase syndrome, advanced sleep phase disorder, jet lag, and shift work sleep disorder [23].

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 [24]. 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, CHF, 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 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 4PM–12MN shift.

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Part IV
Cardiac

Chapter 15
Hypertension

Jitendra Barmecha

Introduction

Hypertension is the most common chronic condition seen in primary care practice. Hypertension is not only a major preventable cause of cardio-cerebrovascular morbidity and mortality; it is also an independent risk factor for end-organ damage including myocardial infarction, stroke, heart failure, retinopathy, and end-stage renal disease. 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 ten 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 three

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_15

American adults also have prehypertension, blood pressure values 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 $48.6 billion each year. This total includes the cost of healthcare services, medications to treat high blood pressure, and missed days of work [2].

Based on the data provided by the American Heart Association in 2015 [3], there is widespread racial and gender disparity in the prevalence of high blood pressure in the US population. 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.

Key History and Physical Exam

Contributing factors to elevated blood pressure need to be assessed during an initial visit and all subsequent visits. Every clinical encounter requires a review of systems and family history of symptoms of cardio-cerebrovascular disease, 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 [4]. Psychosocial and environmental factors that may elevate blood pressure such as social determinants, family situation, employment status, working conditions, and education level need to be addressed. Sodium intake, alcohol use, and intake of saturated fat and cholesterol should be assessed. Medication history should include effectiveness of prior therapy and/or intolerance to previous

antihypertensive therapy and use of commonly prescribed over-the-counter medications, herbal 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, normal BMI, no family history, and presence of end-organ damage and/or dysfunction should be evaluated for secondary hypertension (Tables 15.1 and 15.2).

Physical Examination

Physical examination establishes the diagnosis and may reveal the severity of disease. The following examination should be performed:

Table 15.1 Classification of blood pressure in adults

Blood pressure	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	And <80
Prehypertension	120–139	Or 80–89
Stage 1 hypertension	140–159	Or 90–99
Stage 2 hypertension	≥160	≥100
Stage 3 hypertension	>180	>110
Isolated systolic hypertension	>140	<90

TABLE 15.2 Categories of secondary hypertension in adults

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 the aorta
Aortic regurgitation
Medications
Oral contraceptives
Erythropoietin
NSAIDS
Corticosteroids
Cyclosporine
Miscellaneous

(continued)

TABLE 15.2 (continued)

Secondary
Pregnancy
Perioperative period
Alcohol withdrawal
Obstructive sleep apnea
Caffeine
Nicotine

- Blood pressure measurements bilaterally to detect and confirm the presence of high blood pressure
- Examination of the eyes including 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 [5]. 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 the 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 the first Korotkoff sound.
- Diastolic BP = disappearance of Korotkoff sounds.
- Neither the patient nor the observer should talk during the measurement.

Laboratory Tests

Baseline tests are recommended to identify those individuals at risk for hypertension or to obtain clues to diagnose secondary hypertension:

- Electrocardiogram
- Urinalysis
- Blood glucose measurement
- Complete blood count

- Measurement of serum potassium, calcium, creatinine levels or estimated glomerular filtration rate
- Fasting lipid profile
- Measurement of urinary albumin excretion or albumin/creatinine ratio

Treatment

The treatment of high blood pressure requires a multipronged approach, which includes lifestyle management and non-pharmacological and pharmacological interventions.

Lifestyle Management

A healthy lifestyle is essential in the management of high blood pressure [7]. Diet, nutrient intake, and physical activity can play an important role in the prevention and treatment of high blood pressure and its associated complications. Dietary modifications include weight loss, reduced salt intake, increased potassium intake, moderation of alcohol consumption, and adhering to a healthy diet.

Diet—Emphasis on intake of vegetables and fruits (8–10 servings/day), whole grains, low-fat dairy products (2–3 servings/day), poultry, fish, legumes, nontropical vegetable oils, and nuts and limited intake of sweets, sugar-sweetened beverages, and red meat are recommended. Recommendation of dietary patterns listed below should take into account personal and cultural food preferences, appropriate calorie intake, and other medical conditions.

- DASH or its variant diet
- US Department of Agriculture diet
- American Heart Association diet

Dietary supplements—Garlic has been shown to have blood pressure-lowering properties and 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—2400 mg/day or less is recommended if the desired BP goal is not achieved.

Potassium—Increase potassium intake to >4.0 gm/day.

Physical activity—Engaging in aerobic physical activity for 3–4 sessions per week lasting on average 40 min per session (moderate to vigorous intensity) or at least 150 min per week of moderate intensity is beneficial in reducing blood pressure.

Weight loss—Losing weight to a body mass index of ≤25 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.

Relaxation techniques—There is sporadic evidence for yoga, transcendental meditation, acupuncture, and biofeedback techniques in lowering blood pressure.

Pharmacological Interventions

In 2014, the Eighth Joint National Committee (JNC 8) released evidence-based recommendations on treatment thresholds, goals, and pharmacological interventions in the management of hypertension in adults [8]. Other medical organizations have published similar recommendations along with lifestyle management including diet.

Pharmacologic treatment should be initiated for adults between the ages of 18 and 60 years, when the systolic pressure

is 140 mmHg or higher or when the diastolic pressure is 90 mmHg or higher with a target systolic pressure less than 140 mmHg and a target diastolic pressure less than 90 mmHg.

Pharmacologic treatment should be initiated for adults 60 years of age and older, when the systolic pressure is 150 mmHg or higher, or when the diastolic pressure is 90 mmHg or higher with a target systolic pressure of less than 150 mmHg and a target diastolic pressure of less than 90 mmHg (Table 15.3).

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. Admission to a non-acute inpatient setting during the measurement year.

Home (Self) and Ambulatory Blood Pressure Monitoring (ABPM)

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 that have

Table 15.3 Choice and indications of antihypertensive medications (Modified with permission from a card developed by Cole Glenn, Pharm D, and James Taylor, Pharm D www.nmhs.net/documents/27JNC8HTNGuidelinesBookBooklet.pdf)

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)	• Metoprolol
• Angiotensin receptor blocker (ARB)	• Bisoprolol
• Thiazide diuretic	• Betaxolol
• Calcium channel blocker (CCB)	• Acebutolol
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		Labetolol (first line), nifedipine, methyldopa
Class	*Choice of medications*	*Comments*
Diuretics	HCTZ 12.5–50 mg, chlorthalidone 12.5–25 mg, indapamide 1.25–2.5 mg	Monitor for hypokalemia
	K^+-sparing diuretics: spironolactone 25–50 mg, amiloride 5–10 mg, triamterene 100 mg	Most side effects are metabolic in nature
	Furosemide 20–80 mg twice daily, torsemide 10–40 mg	Most effective when combined with ACEI
		Stronger clinical evidence with chlorthalidone.
		Spironolactone-induced gynecomastia and hyperkalemia
		Loop diuretics may be needed when GFR <40 mL/min

(continued)

TABLE 15.3 (continued)

Initial drugs of choice for hypertension		Beta-1 selective beta-blockers (BB)
ACEI/ARB	*ACEI*: lisinopril, benazepril, fosinopril, and quinapril 10–40 mg, ramipril 5–10 mg, trandolapril 2–8 mg	Side effects: cough (ACEI only), angioedema (more with ACEI), hyperkalemia
	ARB: candesartan 8–32 mg, valsartan 80–320 mg, losartan 50–100 mg, olmesartan 20–40 mg, telmisartan 20–80 mg	Losartan lowers uric acid levels; candesartan may prevent migraine headaches
Beta-blockers	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	Cause edema; dihydropyridines may be safely combined with a beta-blocker
	Non-dihydropyridine: diltiazem ER 180–360 mg, verapamil 80–120 mg three times daily, or verapamil ER 240–480 mg	Non-dihydropyridines reduce heart rate and proteinuria
Vasodilators	Hydralazine 25–100 mg twice daily, minoxidil 5–10 mg once daily	Hydralazine and minoxidil may cause reflex tachycardia and fluid retention—usually require diuretic + BB
	Terazosin 1–5 mg, doxazosin 1–4 mg given at bedtime	Alpha-blockers may cause orthostatic hypotension
Centrally acting agents	Clonidine 0.1–0.2 mg twice daily, methyldopa 250–500 mg twice daily	Clonidine available in weekly patch formulation for resistant hypertension

been recommended such as self- or home monitoring and ambulatory blood pressure monitoring. 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 antihypertensive therapies [9]. 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. For both self- and ambulatory blood pressure monitoring, monitors that use the upper arm are better than the wrist, except in very obese individuals. Finger devices are not reliable. An up-to-date list of monitors can be retrieved from www.dableducational.org [10]. Currently, ABPM is not widely used in clinical practice, mainly because the expenses are often not reimbursed by payors, but this will change as healthcare moves toward a value-based reimbursement system (Figs. 15.1 and 15.2) (Table 15.4).

Refractory or Resistant Hypertension

Refractory or resistant hypertension is defined as a blood pressure of at least 140/90 mmHg despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic [11].

In order to diagnose refractory hypertension, various factors that need to be considered are secondary causes of hypertension (Table 15.2), improper blood pressure measurement, volume overload, competing substances, obesity, nonadherence to treatment, inadequate doses or inappropriate combinations of medications, and alcohol consumption [12] (Fig. 15.3).

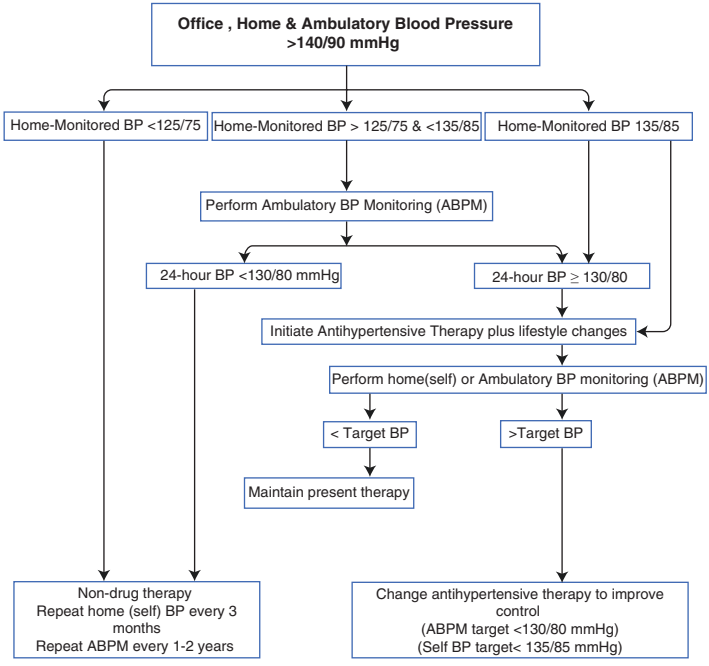

FIG. 15.1 Practical use of home (self) BP monitoring and ambulatory blood pressure monitoring (ABPM). Home (self) BP monitoring should be performed according to strict guidelines prior to clinical decision-making. Following initiation of antihypertensive therapy, the determination to use home (self) BP monitoring vs. ABPM is made according to availability, clinical judgment, and insurance coverage

Role of Digital Health in Hypertension

Digital health interventions for hypertension include blood pressure sensors, 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 healthcare providers, and medication reminder alerts. With increasing emphasis on home and ambulatory blood pressure monitoring to confirm

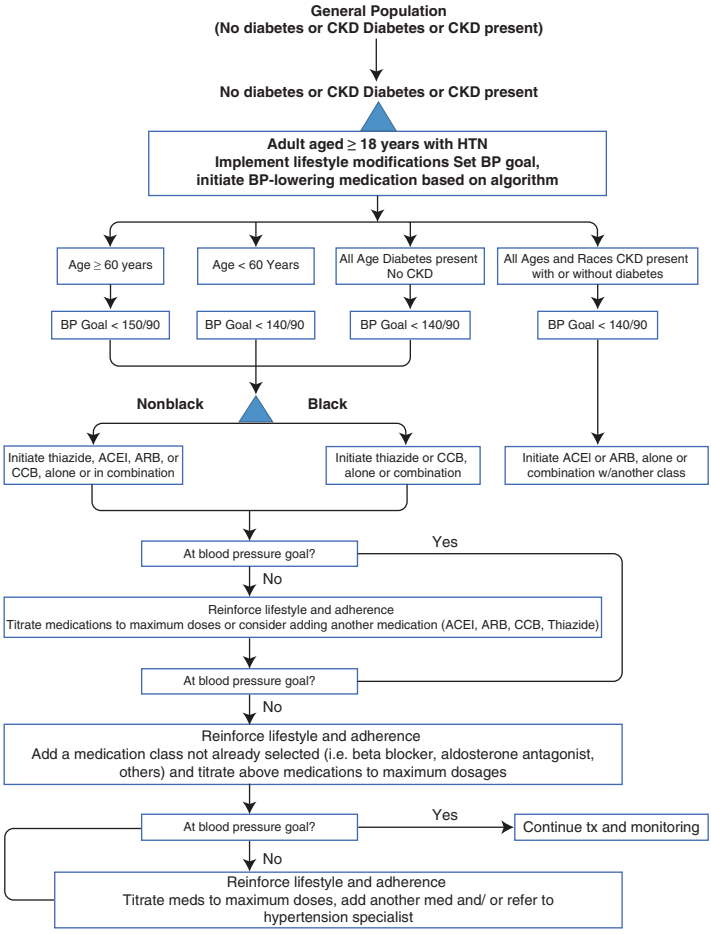

FIG. 15.2 JNC 8: evidence-based guideline for the management of high blood pressure in adults [6]

TABLE 15.4 Blood pressure patterns that can be determined by office BP, ambulatory blood-pressure monitoring (ABPM), and home (self) BP measurements

Blood pressure	Office BP	ABPM	Home (self)
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

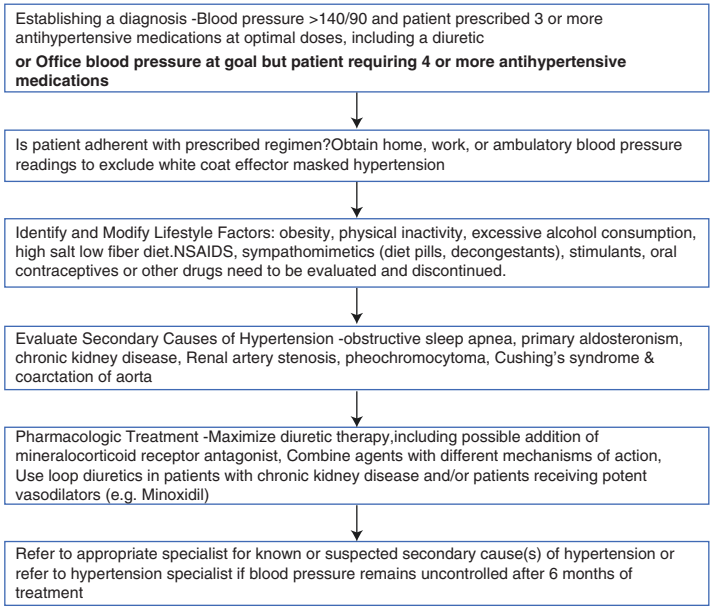

FIG. 15.3 Refractory or resistant hypertension: management algorithm

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 infarction, stroke, heart failure, retinopathy, and end-stage renal disease.
- 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, isolated diastolic, or both systolic and diastolic.
- Secondary causes of hypertension should be assessed when resistant hypertension is present.
- Ambulatory blood pressure monitoring is a useful tool in the management of hypertension.
- The antihypertensive medications ACE inhibitors, angiotensin receptor blockers (ARBs), and renin inhibitors 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 16
Chest Pain

Magda M. Amer

Introduction

Chest pain is a diagnostic challenge given the wide array of possible etiologies. Chest pain is caused by conditions that range from benign and self-limited (e.g., chest wall pain, anxiety) to serious or life threatening (e.g., unstable angina, aortic dissection, and pulmonary embolism). Accurate identification of life-threatening and serious causes of chest pain must be accomplished expeditiously in the primary care setting [1].

Key History and Physical Exam

When assessing a patient with chest pain, the history should address the following characteristics:

- *Onset* of chest pain—sudden or gradual
- *Location* of chest pain—left side, retrosternal, epigastric, or right side.

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_16

- *Radiation* of pain—to the neck, throat, lower jaw, teeth, or shoulder.
- *Quality* of chest pain—pleuritic, positional, sharp, dull, ripping, tearing, reproducible with palpation.
- *Exacerbating factors*: exertion, cold, emotional stress, meals, or sexual intercourse.
- *Associated symptoms*: nausea, diaphoresis, palpitations, orthopnea, fever, chills, productive cough, heartburn, dysphagia, trauma, or weight loss.

The physician should focus on past history of similar chest pain, cardiac disease, hypertension, diabetes, and hyperlipidemia. Family history of coronary artery disease, clotting history, and smoking history should be elicited.

Vital signs are a critical component of the physical examination of a patient presenting with chest pain. Hypoxia, tachycardia, hypotension, or hypertension may indicate pulmonary or cardiac causes. Fever and hypoxia may indicate infection such as pneumonia. Blood pressure should be checked in both arms to identify the possibility of aortic dissection.

Inspect the chest and upper abdomen for abnormal pulsations, abnormal patterns of breathing, or external physical injuries. Palpate for localized tenderness. Auscultate the lungs for any abnormal lung sounds (e.g., crackles, wheezing, asymmetric breath sounds). Auscultate the heart noting any abnormal or extra heart sounds (e.g., murmurs, s3/s4 gallop).

Gender and Cardiac Disease Presentation

The epidemiology has shown that the clinical manifestation and the progression of coronary artery disease are different in both sexes. Women develop cardiovascular disease about 10–20 years later than men, partly by the influence of hormones and partly by the genetic sex.

At the time of the first episode of an acute myocardial infarction, women are more likely to have diabetes mellitus or heart failure compared to men [2].

Several studies have indicated that women have “atypical” symptoms such as back pain, dyspnea, indigestion, nausea/

vomiting, and weakness. Frequently, women report pain in the jaw and neck and describe their symptoms with more of an emotional component compared with men [2].

The atypical presentation may explain the rate of underdiagnosed acute myocardial infarction in women. Overall women are undertreated for acute coronary syndromes and have worse outcomes characterized by increased hospital morbidity, higher mortality, and fewer evidence-based therapies [3].

For these reasons above, it is vital that the primary care physician carefully evaluate any female patient presenting with GI type symptoms as they may be presenting with cardiac ischemia.

The sensitivity of noninvasive diagnostic tests is lower in ECG exercise stress test in women compared to men because of the higher incidence of false-positive ST-segment depression during exercise and inadequate exercise to induce ischemia during stress testing, especially among elderly women [4].

For women with typical or atypical chest pain, stress echocardiography and stress nuclear imaging are the noninvasive modalities of choice for detecting coronary artery disease [4].

- *Differential Diagnosis*: (see Table 16.1) (Fig. 16.1)

Cardiac Causes:
Chest pain due to cardiac ischemia typically tends to be retrosternal or epigastric and tight and crushing in quality and may radiate to the arms, shoulders, neck, or jaw.

Stable angina is likely if chest discomfort or dyspnea is associated with effort, emotion, food, or cold weather and if the symptoms are stable in character (e.g., onset and duration of symptoms have been consistent over time). Stable angina symptoms generally last for minutes and are relieved by rest and/or NTG (nitroglycerin).

Unstable angina/myocardial infarction is defined as a new pattern of chest pain or a worsening pattern of an existing chest pain or dyspnea.

Noncardiac Causes:
Aortic dissection tends to cause pain with a tearing quality that may radiate to the back.

TABLE 16.1 Chest pain causes

Cardiac causes	Vascular causes	Pulmonary causes	Gastrointestinal causes	Musculoskeletal causes
Acute coronary syndrome	Acute aortic dissection	Pulmonary embolism	GERD	Costochondritis
Stable angina	Primary pulmonary hypertension	Pneumothorax	Esophageal spasm	Chest wall pain
		Pneumonia	Gastritis	
		Pleurisy	Peptic ulcer/biliary colic	

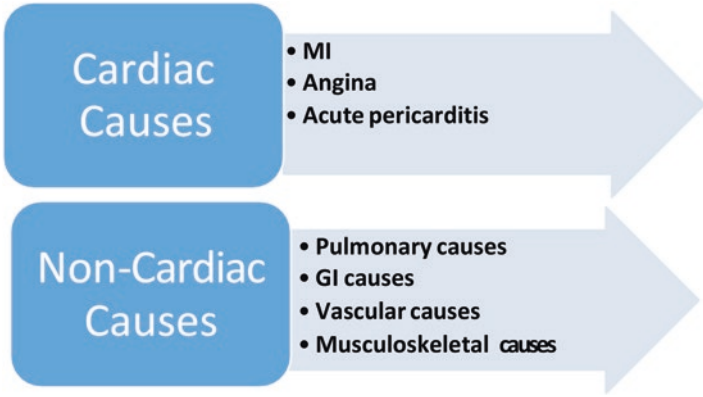

FIG. 16.1 Chest pain causes

Pericarditis pain tends to be worse on inspiration (pleuritic) and improves with sitting up and leaning forward.

Pulmonary embolus causes breathlessness (may be acute or slower onset) and sharp chest pain worse on inspiration and may be associated with hemoptysis and/or syncope.

Pleurisy causes sharp, localized chest pain, worse on inspiration.

Pneumothorax causes sudden onset of pleuritic chest pain or increased breathlessness with or without pallor and tachycardia.

Esophageal spasm or gastroesophageal reflux disease (*GERD*) pain is usually centrally located in the chest and may be associated with acid reflux.

Gallstones may present with right-sided chest pain with radiation to the shoulder.

Acute pancreatitis may present with central chest pain, although it is usually accompanied by epigastric tenderness.

Musculoskeletal pain is usually localized pain, worse on movement and reproducible with external compression.

Costochondritis is inflammation of the costochondral junctions, which manifests as localized tenderness over the costochondral junction on palpation of the chest wall.

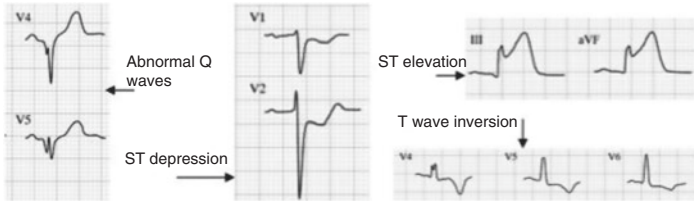

FIG. 16.2 ECG changes associated with ischemic heart disease

- *Decision-Making*

Assessment of chest pain in primary care is difficult. There is no need to admit every patient with chest pain, but caution is needed to prevent missing significant and serious disease.

Blood Tests:

Helpful blood tests to include are a complete blood count to exclude anemia and as an indicator of infection, urea and electrolytes, fasting glucose, d-dimer and a fasting lipid profile.

ECG (*Electrocardiogram*):

ECG is indicated to identify signs of ischemia (e.g., abnormal Q waves, ST elevation or depression, abnormal T waves—see Fig. 16.2). ECG may also identify arrhythmias and evidence of left ventricular hypertrophy.

Imaging

Consider a chest X-ray to assess cardiac size or exclude pneumonia or pneumothorax.

Management depends on suspected differential diagnosis. Table 16.1 lists the common differential diagnoses of acute chest pain in primary care. Evaluating symptomatology in conjunction with risk factors (see Table 16.2) and modifiable risk factors (see Table 16.3) can help to predict likelihood of a cardiac etiology.

Table 16.2 Risk factors

Age 55 years or older in men; 65 years or older in women
Known CAD or cerebrovascular disease
Pain not reproducible by palpation
Pain worsens during exercise
Patient assumes pain is cardiogenic

Table 16.3 Modifiable risk factors

Smoking
Diabetes mellitus/ hypertension
Dyslipidemia/obesity
Alcohol consumption
Psychosocial stressors
Physical activity/diet

Cardiac stress testing is an important diagnostic and prognostic tool in the evaluation and management of patients.

The following patients should be referred for stress testing on presentation:

- Symptoms suggesting angina
- Known CHD (coronary heart disease) and new or worsening symptoms
- Prior coronary revascularization CABG (coronary artery bypass grafting) >5 years or percutaneous coronary intervention >2 years
- Chronic left ventricular dysfunction and CHD in patients who are candidates for revascularization (Fig. 16.3; Table 16.4)

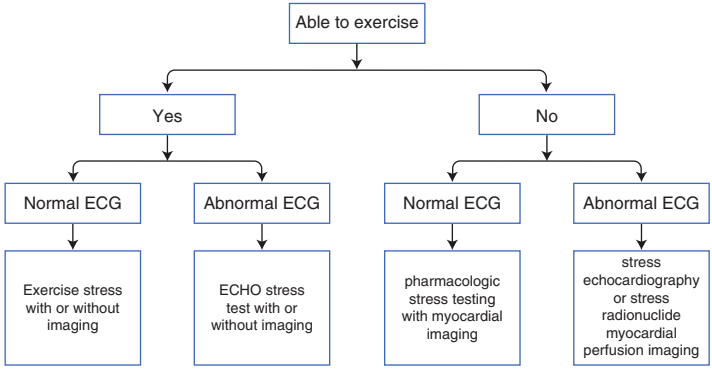

FIG. 16.3 Approach to choosing the optimal stress test

TABLE 16.4 Sensitivity and specificity for detecting coronary artery disease

Test	Sensitivity (%)	Specificity (%)
Exercise treadmill ECG test	45–61	70–90
Exercise nuclear perfusion imaging	73–92	63–88
Dobutamine stress myocardial perfusion imaging	88–91	75–90
Exercise echocardiography	70–85	77–89
Dobutamine stress echocardiography	72–90	79–95
Coronary CTA (not widely used)	93–90	64–90

Adapted from Heart Int. 2012; 7(1):e2. [6]
CTA computed tomography angiogram

- Preoperative evaluation for non-cardiac surgery in patients deemed to be at high risk [5]
- *Treatment*

Unstable Angina

In patients with chest pain with or without new ECG changes (ST or Q waves) and high to moderate cardiac risk (Table 16.2), give aspirin 162–325 mg by mouth, oxygen, and NTG, obtain IV access, do cardiac monitoring and blood work which includes cardiac enzymes, and refer to the ER. Patients with chest pain and no ECG changes and low cardiac risk may be referred for outpatient stress testing. See Fig. 16.4.

Stable Angina

In patients with stable ischemic heart disease, the first-line therapy to reduce anginal episodes and improve exercise tolerance is beta-blockers. Furthermore, beta-blockers are the only antianginal medication shown to prevent reinfarction

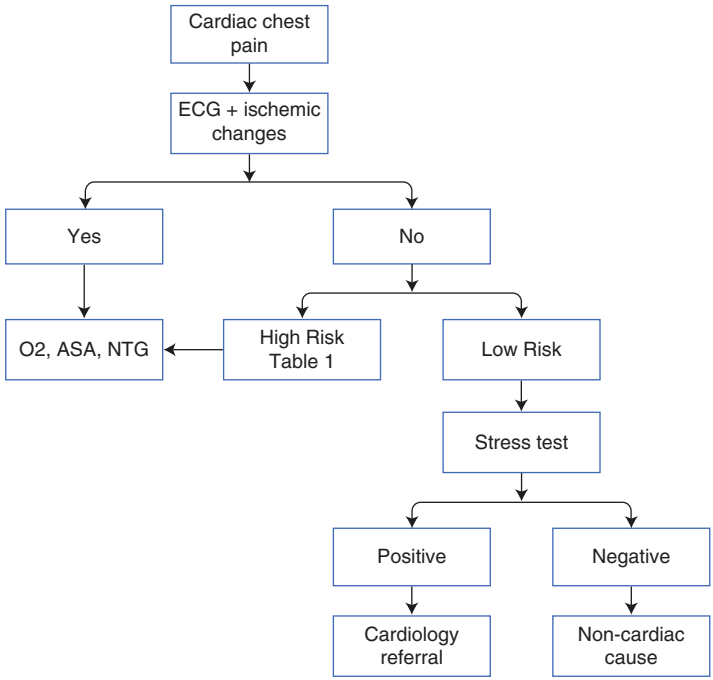

FIG. 16.4 Clinical approach for cardiac chest pain

and to improve survival in patients who have already had a myocardial infarction [7].

Nitrates should be used for relief of acute anginal symptoms, and they may also help to prevent recurrent angina episodes through coronary vasodilation.

All patients should be treated with aspirin in doses from 75 to 325 mg provided there is no contraindication to antiplatelet therapy.

Ranolazine, a piperazine derivative, was approved by the FDA in 2006 as a new antianginal agent to treat chronic stable angina. It is intended for use as combination therapy when angina is not adequately controlled with other antianginal agents [8].

The following patients should be referred to the emergency room:

- Aortic dissection: unequal blood pressures bilaterally
- Pneumonia: fever and cough, infiltrates on chest X-ray, Curb 65 score ≥ 2
- Pneumothorax: decreased lung sounds unilaterally. Changes in fremitus and percussion. Diagnosis made by chest X-ray
- Pulmonary embolism: hemoptysis and dyspnea in a patient with risk factors

Young patients with low cardiovascular risk presenting with heartburn, and epigastric pain, may be sent home with an antacid and followed up after 2–3 weeks. Patients who have a low cardiovascular risk, are afebrile, and present with localized pain and tenderness, may be managed with NSAIDs and pain control for costochondritis. See Fig. 16.5.

Clinical Pearls

- Comprehensive history and examination are vital to the diagnosis.
- Consider the differential diagnosis when interpreting symptoms and signs and investigating results.
- Evaluate risk factors for cardiac disease when assessing a patient.

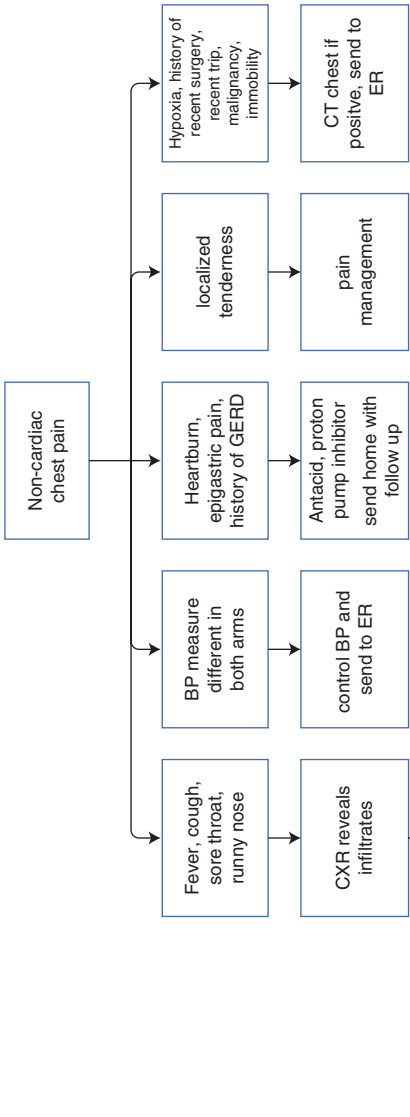

FIG. 16.5 Clinical approach for noncardiac chest pain

Don't Miss This!

- If a patient is acutely unwell with chest pain and the cause is not clear, err on the side of caution and send the patient to ER for further assessment.
- Remember that women can present atypically with cardiac ischemia that may mimic GI distress.

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Chapter 17
Anemia

Niraj K. Shenoy and Hernando J. Cordero

Introduction

The diagnosis and initial evaluation of anemia is an important aspect of the internist's office practice. This chapter provides an algorithm-based approach to help guide the internist through the differential diagnoses and decision-making process.

Key History and Physical Exam

Primary care physicians should focus their evaluation toward obtaining clues useful for accurate diagnosis of anemia and its etiology. Key questions include the following: Any evidence of blood loss? What is the duration of the anemia? Is this

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_17

genetic or acquired? Is infection or malignancy likely? Are there associated features or comorbidities known to cause anemia (e.g., renal failure, rheumatoid arthritis, and inflammatory bowel disease)? Does the patient's ethnicity influence the differential? A careful review of medications, including the use of aspirin and nonsteroidal anti-inflammatory drugs, needs to be performed.

Classic symptoms that must be addressed include bleeding, fatigue, fever, weight loss, night sweats, and signs of infection.

Physical examination can reveal tachycardia, hypotension in acute blood loss, conjunctival pallor, jaundice, strong peripheral pulses, systolic blood flow murmur, lymphadenopathy, hepatosplenomegaly, bone tenderness, petechiae, and ecchymoses.

Diagnosis and Evaluation

- CBC (complete blood count) initial variables to review: hemoglobin (Hgb), hematocrit (Hct), corpuscular volumes [mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)], red blood cell (RBC) count, red cell distribution width (RDW), platelet count, and white blood cell (WBC) count with differential.
- Reticulocyte count to calculate the reticulocyte index and determine the nature of the anemia: hypoproliferative or hyperproliferative.
- Iron storage/supply [serum iron, total iron-binding capacity (TIBC), serum ferritin].
- Abnormalities in direct and indirect bilirubin, lactate dehydrogenase (LDH), and haptoglobin will suggest a hemolytic process.
- Peripheral blood smear: detailed evaluation for evidence of variations in cell size (anisocytosis) and cell shape (poikilocytosis).
- In some patients more advanced testing, such as hemoglobin electrophoresis and bone marrow examination (smear and aspirate), is warranted (Fig. 17.1).

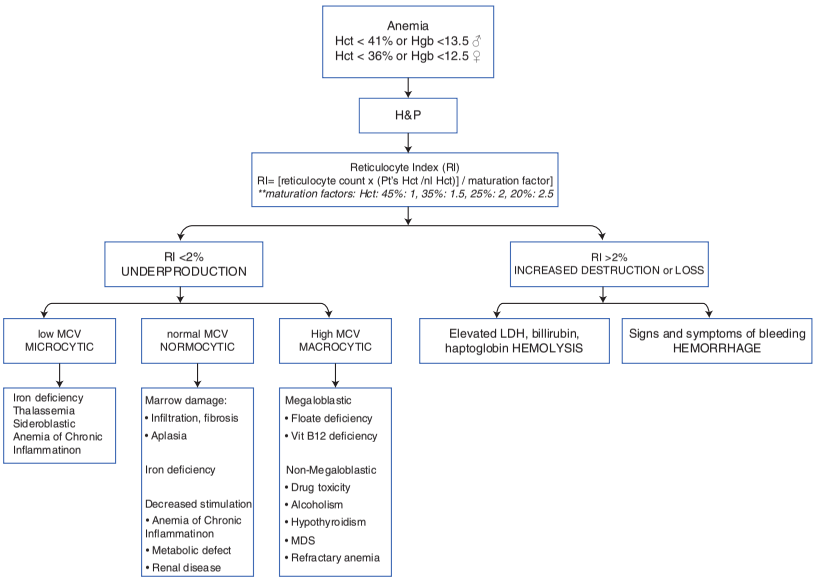

FIG. 17.1 Anemia algorithm

Hypoproliferative Anemias

The reticulocyte index is <2% in hypoproliferative anemia.

Microcytic Anemias

These are characterized by smaller RBCs (MCV < 70) due to decreased production of hemoglobin. Common causes are lack of globin production (thalassemia), restricted iron delivery to the heme group (inflammation), lack of iron delivery to the heme group (iron-deficiency anemia), and defects in the synthesis of the heme group (sideroblastic anemia) [1]. Iron studies will guide us toward the most likely etiology, as shown in the following Table 17.1.

Iron-Deficiency Anemia

Iron deficiency is the most common cause of anemia and is estimated to be present in 1–2% of the adult population. Iron deficiency in the absence of anemia is present in up to 11% of the adult population [2]. Decreased marrow iron and depleted iron stores cause decreased heme synthesis, leading to microcytosis and anemia.

In addition to general anemia symptoms, specific iron deficiency manifestations can include pica and pagophagia, brittle integument, and restless leg syndrome.

Serum ferritin level is the most sensitive and specific test used for the identification of iron deficiency (level of <12 ng/mL). In those with combined inflammation and iron deficiency, ferritin may be falsely elevated because it is an acute-phase reactant. Soluble transferrin receptor is not affected by inflammatory states and is a useful test to determine the presence of iron deficiency. If erythroid precursor cells have cellular iron deficiency, they express increased transferrin receptors to attract the iron-carrying transferrin. Some of these transferrin receptors then spill out in the

TABLE 17.1 Iron studies in microcytic anemia

	Serum iron	TIBC	Transferrin saturation	Serum ferritin
Normal range	40–180 ug/dL	205–450 ug/dL	25–35%	18–300 ng/mL
Iron deficiency	Low < 40 ug/dL	High > 350 ug/dL	<15%	Low <12 ng/mL
Anemia of chronic disease	Low < 40 ug/dL	Low < 300 ug/dL	>15%	Normal–high
Thalassemia	Normal to high	Normal to high	Normal >30%	Normal–high
Iron overload (hemosiderosis)	High	High	>45%	Increased

blood and are detected [3]. A transferrin saturation level of less than 16% indicates an iron supply that is insufficient to support normal erythropoiesis [3].

The most frequent causes of iron-deficiency anemia are:

- Chronic GI bleeding, often subclinical, due to gastric ulcerations, GI malignancies.
- Decreased iron absorption: malnutrition, vegan diet, celiac sprue, inflammatory bowel disease (Crohn's), gastrectomy/bariatric surgery, increased gastric pH, or use of chronic gastric acid suppressants.
- States with increased iron demand, i.e., pregnancy, rare iron refractory genetic disorders.

Treatment

Replacing iron and correcting the underlying etiology are the cornerstones of therapy. After 1 week of treatment, reticulocytosis should begin. In 3 weeks, Hgb should be 2 g/dL higher. Iron supplementation should continue not only until Hgb level is normalized, but until iron stores are repleted, typically after 6 months of therapy. Repletion can be confirmed when serum ferritin normalizes.

Oral supplementation is preferred; however, IV iron preparations can be given to patients with high Fe requirements, inability to absorb Fe from GI tract, or intolerance to oral iron preparations.

Preferred oral iron replacement:

- Ferrous sulfate 325 mg orally: For best absorption and tolerability, take 30 min before meals. Can start with 1 tab/day and increase up to three times per day. If unable to take three times per day, 1–2 times per day may be sufficient as long as the Hgb is recovering.
- Adverse effects: bloating, change in bowel habits, black stools.

Refractoriness to treatment should raise the concern of compliance issues, poor absorption, and possibly incorrect diagnosis (e.g., thalassemia, anemia of chronic inflammation).

Normocytic Anemia

There is an overlapping of some anemias with normal MCV which might be either hypoproliferative or hyperproliferative, but could also present as normocytic, microcytic, or macrocytic. This category includes acute blood loss/hemorrhagic anemia, anemia of renal disease, hypothyroidism, early stages of iron deficiency, anemia of chronic inflammation, sickle cell anemia, pure red cell aplasia as seen in thymomas, chronic lymphocytic leukemia, and parvovirus infection.

Anemia of Chronic Inflammation (ACI)

Previously known as anemia of chronic disease, this is the second most common form of anemia after iron deficiency. Classically, it was thought to be caused only by inflammatory, infectious, or malignant processes; however, diabetes and severe trauma have also been proposed etiologies. Major causes include malignancy, HIV infection, rheumatologic disorders, inflammatory bowel disease (Crohn's), heart failure, renal insufficiency, and chronic obstructive pulmonary disease.

The underlying process is multifactorial. It involves increased pro-hepcidin, an acute-phase reactant, causing decreased intestinal absorption of iron and trapping of iron in the macrophages resulting in decreased availability for heme synthesis. Also, there is an inability to increase erythropoiesis, relative decrease in erythropoietin (EPO) production, and RBC survival. These changes are mediated by inflammatory cytokines, TNF-alpha, IL-1, IL-6, INF-b, and INF-g.

Patients with anemia of chronic disease and concomitant iron-deficiency anemia more frequently have microcytes, and their anemia tends to be more severe. The ratio of the concentration of soluble transferrin receptors to the log of the ferritin level of less than 1 suggests anemia of chronic disease,

whereas a ratio of more than 2 suggests absolute iron deficiency coexisting with anemia of chronic disease [3].

The primary treatment of ACI is correction of the underlying disorder. Blood transfusions are only indicated in the setting of severe symptomatic anemia Hgb < 6.5 mg/dL or acute bleeding. Transfusion affords some benefit in survival for patients with myocardial infarction.

Iron supplementation might be beneficial if ferritin or TIBC saturation is low or low normal.

EPO can be administered if EPO level is < 500 mU/mL and Hgb <10 g/dL for cancer or chemo-related ACI.

Macrocytic Anemia

Macrocytic anemia is defined by an MCV > 100, and can be categorized as megaloblastic or non-megaloblastic depending on the presence of hypersegmented neutrophils in addition to macrocytic RBCs in the peripheral smear [4].

Megaloblastic Anemia

Resulting from impaired DNA synthesis, megaloblastic anemia is usually caused by folate or vitamin B12 (cobalamin) deficiency, which in turn could be due to chemotherapeutic agents that impair absorption or block enzymes during DNA synthesis.

Vitamin B12 Deficiency

Always establish a cause of vitamin B12 deficiency. Major causes include pernicious anemia, atrophic gastritis, bacterial overgrowth, pancreatic insufficiency, ileal resection or Crohn's disease involving the ileum, chronic proton pump inhibitor or histamine 2-blocker use, HIV, *Helicobacter*

pylori, and *Diphyllobothrium latum* (fish tapeworm) infections.

Common signs and symptoms of B12 deficiency include general symptoms of anemia, beefy tongue, and neurologic symptoms due to degeneration of the lateral and dorsal columns of the spinal cord known as subacute combined degeneration (SCD). Symptoms of SCD include paresthesias from axonal degeneration, cerebellar ataxia, proprioceptive deficit, and dementia.

Laboratory findings include low serum B12 level (<200 very suggestive, 200–400 borderline), along with elevated methylmalonic acid (MMA) and homocysteine levels, macrocytosis, pancytopenia, and hypersegmented neutrophils. If MMA is normal, significant B12 deficiency is unlikely.

Treatment of severe cases is supplementation of B12 by injection of 1000 mcg daily for 5 days, then monthly. Oral B12, dosed at 500–1000 mcg daily, is usually absorbed well enough even in patients with atrophic gastritis, gastric resection, or pernicious anemia.

Folate Deficiency

Folate deficiency is most commonly caused by poor dietary ingestion. Other causes are malabsorption (sprue), and hemolytic anemia.

In B12 deficiency neurologic abnormalities can be present and MMA is elevated.

However, in folate deficiency neurologic abnormalities are absent and MMA is normal, and homocysteine is increased. RBC folate levels rather than serum folate levels are more accurate for diagnosing deficiency.

Treatment is to give folate 1 mg/day even if deficiency is caused by malabsorption.

Non-megaloblastic anemia: Other causes of macrocytic anemias without megaloblastosis include:

- Liver disease
- Alcohol abuse (even in the absence of vitamin B12 or folate deficiency)
- Hypothyroidism
- Smoking
- Drugs (hydroxyurea, antiretrovirals, 5-FU, azathioprine, etc.)
- Primary bone marrow disorders
- Reticulocytosis

Hyperproliferative Anemias

Hyperproliferative anemias are the result of acute blood loss or increased RBC destruction such as in hemolysis, which may be due to congenital or acquired causes. Aside from blood loss, hyperproliferative anemias warrant a referral to a hematologist given the complexity of management.

Defects in Red Cell Membrane

Hereditary spherocytosis is characterized by osmotically fragile spherical red blood cells due to a deficiency of one of the membrane proteins. Spherocytes have diminished deformability, predisposing them to entrapment and destruction in the spleen.

Patients present with evidence of hemolysis (anemia, jaundice, reticulocytosis, gallstones, splenomegaly) with spherocytosis (spherocytes on the peripheral smear and increased osmotic fragility) and a positive family history.

Peripheral smears usually show easily identifiable spherocytes lacking central pallor.

Treatment includes folic acid supplementation (1 mg/day) and splenectomy for moderate to severe cases. Ultrasound should be carried out before splenectomy to exclude the presence of gallstones. If present, cholecystectomy is also indicated [5].

Defects in Red Blood Cell Metabolism

Glucose-6-phosphate dehydrogenase deficiency (*G6PD*) diminishes the reductive energy of the red cell affecting red cell integrity when exposed to certain drugs, infections, chemicals, and fava beans, resulting in hemolysis.

Oxidized hemoglobin precipitates to form Heinz bodies which are plucked out of the red cell leading to hemolysis and "bite cell" and "blister cell" morphology [6].

Patients require education about foods (e.g., fava beans) and drugs (e.g., quinolones, sulfa, and certain antimalarials) that should be avoided. Patients should be aware of the signs of hemolytic crisis (orange/dark urine, lethargy, fatigue, jaundice) and be hypervigilant during acute infections. Patients should be transfused with packed red blood cells if Hb level is below 7 g/dl or if hemoglobinuria persists and Hb is below 9 g/dL [7].

Hemoglobinopathies

Sickle Cell Disease

Sickle cell disease is the most commonly observed hemoglobinopathy in the United States, affecting 1:500 African-American births and 1:36,000 Hispanic-American births.

The defect is a Glu → Val substitution in the sixth amino acid of the β-globin gene producing mutant β-globins that form hemoglobin S which polymerizes resulting in deformed RBCs. Sickle cells are prematurely destroyed or hemolyzed which reduces nitric oxide (NO) bioavailability contributing to vasoconstriction and platelet activation. This cascade of events causes endothelial damage, production of inflammatory mediators, and overexpression of adhesion molecules producing vaso-occlusion and stasis [8].

Always be aware of the three main types of complications of sickle cell anemia:

- Hemolysis associated: severe anemia, cholelithiasis, acute aplastic episodes (parvovirus B19 infection), pulmonary hypertension
- Infectious complications: *Streptococcus pneumoniae*, *E. coli* sepsis, osteomyelitis (*Salmonella*)
- Vaso-occlusive: painful crises, acute chest syndrome, splenic sequestration/infarcts, stroke, osteonecrosis of the bone, priapism, leg ulcers, spontaneous abortion, renal insufficiency

Management of Common Acute Complications

Vaso-occlusive crisis (VOC): In patients with mild-to-moderate pain who report relief with NSAIDS, continue the same treatment in the absence of contraindications. In severe pain, hospitalization for pain control is indicated.

Fever: If temperature ≥101.3 °F (38.5 °C), evaluate with H&P, CBC with differential, reticulocyte count, blood culture, and urine culture when urinary tract infection is suspected [9].

Hospitalize if acute chest syndrome (acute onset of lower respiratory tract disease with cough, shortness of breath, tachypnea, retractions, or wheezing with or without fever), stroke, priapism lasting >4 h, acute pain requiring parenteral opiates, or fever with temperature ≥103.1 °F (39.5 °C). Chronic complications include chronic pain, leg ulcers, avascular necrosis, pulmonary hypertension, and renal and ophthalmologic complications [9].

Outpatient treatment focuses on prevention of acute and chronic complications of sickle cell anemia.

Patients should be treated with hydroxyurea under the following conditions: three or more sickle cell severe pain crises in a 12-month period; pain that interferes with daily activities and quality of life, severe and/or recurrent ACS; or severe symptomatic chronic anemia. Hydroxyurea should be discontinued if the patient becomes pregnant or is breastfeeding. The starting dosage for adults (500 mg capsules) is 15 mg/kg/day. The dosage should be reduced to 5–10 mg/kg/day if the patient has chronic kidney disease [9].

Health maintenance includes vaccination against *Streptococcus pneumoniae* and regular screening for hypertension, proteinuria, and retinopathy [9].

Thalassemias

In this type of anemia, there is decreased synthesis of structurally normal globin proteins, characterized by low Hgb and unusually small and fragile RBCs (microcytosis), although the RBC count may be normal. In thalassemia minor, the RBC count is usually high and the Hgb and RDW will be normal or slightly abnormal. Subtypes of thalassemia involve imbalances in the four chains of amino acids that comprise hemoglobin (alpha- and beta-globins). This causes instability in the globin chains, which precipitate in RBC precursors in the bone marrow, leading to ineffective erythropoiesis and microcytic anemia:

- Decreased α synthesis = α thal → relative excess of β globins
- Decreased β synthesis = β thal → relative excess of α globins

Although thalassemia major is a serious disease, in adult medicine we see thalassemia minor, which requires no treatment:

- *Beta thalassemia minor*: generally asymptomatic; mild microcytic anemia
- *Alpha thalassemia minor*: lifelong mild microcytic anemia, microcytosis out of proportion to the degree of anemia, high RBC count [10]

Hemolytic Anemia

The reticulocyte index will be >2% (see algorithm). Based on the underlying pathophysiologic process, hemolytic anemias can be classified as immune and non-immune mediated:

- *Immune mediated* (Coombs positive)
- In addition to recent history of blood transfusions or specific drug use, further workup needs to be done to determine the following:

1. Autoimmune (warm or cold).
2. Alloimmune (acute or delayed transfusion reaction).
3. Drug induced (e.g., quinidine, phenacetin, INH, hydralazine, sulfa drugs, penicillin, methyldopa, dapsone, nitrites, rifampin). Patients with G6PD deficiency are particularly prone.

- *Non-immune mediated* (Coombs negative)—intravascular hemolysis due to:

1. Microangiopathic hemolytic anemia
2. Defects in RBC membrane/enzymes
3. Infections (bacterial, viral, or fungal)

Usually hemolytic anemia is normocytic, but can be macrocytic if there is significant reticulocytosis. Testing includes LDH, indirect bilirubin, haptoglobin, urinary-free hemoglobin (if brisk intravascular hemolysis, positive dipstick, but no RBC on urine analysis), and Coombs (direct antiglobulin test or DAT) test.

Microangiopathic hemolysis produces schistocytes on smear due to mechanical intravascular disruption of RBCs.

Always send a preliminary panel of hemolysis labs for any unexplained normocytic anemia (or macrocytic with high reticulocyte count). Without a high index of suspicion, subtle hemolysis can be missed.

Clinical Pearls

Categorize anemia based on reticulocyte index and cell size.

Anemia can have more than one etiology in the same patient.

Acute treatment of anemia should be based on symptoms, not Hgb level.

Don't Miss This!

Test for gastrointestinal cancer in all patients older than 50 years of age with microcytic anemia.

Think of hemolysis with unexplained normocytic anemia.

B12 deficiency is a reversible cause of dementia.

Acknowledgment The authors would like to acknowledge Dr. Naseema Gangat's valuable input and edits. Dr. Gangat is a staff hematologist at Mayo Clinic, Rochester, in charge of the hematology education curriculum for the Internal medicine residents at Mayo Clinic.

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Chapter 18
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

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_18

and plasma. The hydrostatic pressure within the capillaries tends to drive fluid out of the capillaries, whereas the oncotic 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, cellulitis, or a ruptured popliteal cyst (Fig. 18.1). In those patients with history of recent trauma or surgery, compartment syndrome should be considered. 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. Lymphedema is usually non-pitting, and the skin has a verrucous aspect. Lastly, obstruction by a tumor or lymphadenopathy can lead to unilateral edema.

Edema related to systemic conditions is often subacute or chronic and bilateral, affects the lower extremities, and on occasion becomes generalized (Fig. 18.1). 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, pulmonary hypertension). Jaundice, ascites, and asterixis are seen with liver disease, and a frothy urine could be a manifestation of underlying kidney disease. 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.

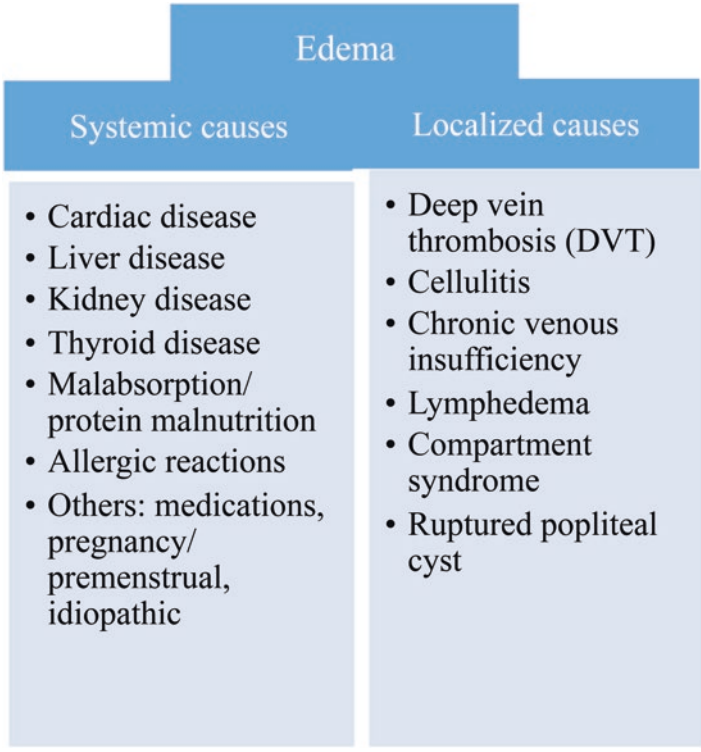

FIG. 18.1 Systemic and localized causes of edema

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. 18.2) [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, chills, or weight loss as well as those suggestive of hypervolemia. The medication list, including over-the-counter

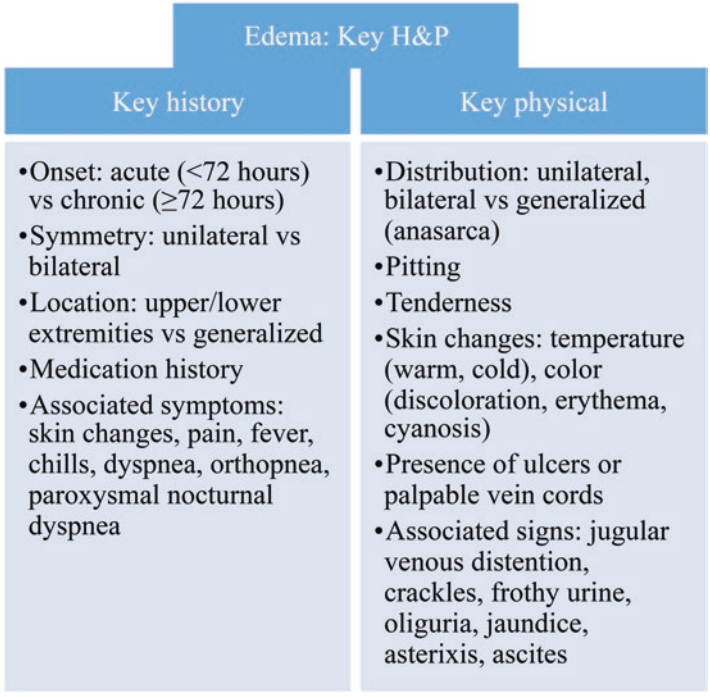

Fig. 18.2 Key history and physical in the evaluation of edema

remedies, should be thoroughly reviewed given that commonly used medications can be associated with edema (Table 18.1).

Physical examination should focus on evaluating the distribution and severity of edema (Fig. 18.2) [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). The Kaposi-Stemmer sign refers to the inability to form a fold on the skin at the base of second toe and is suggestive of lymphedema [2, 8]. The skin should be thoroughly evaluated describing its color, temperature, and presence of ulcers or palpable vein cords. The sys-

Table 18.1 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

temic 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 with unilateral edema concerning for DVT (Fig. 18.3), a D-dimer and venous ultrasound can be part of the initial evaluation depending on the level of clinical suspicion [9]. 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. 18.4). Thyroid-stimulating hormone can also be included if there is suspicion for thyroid disease. Duplex 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-

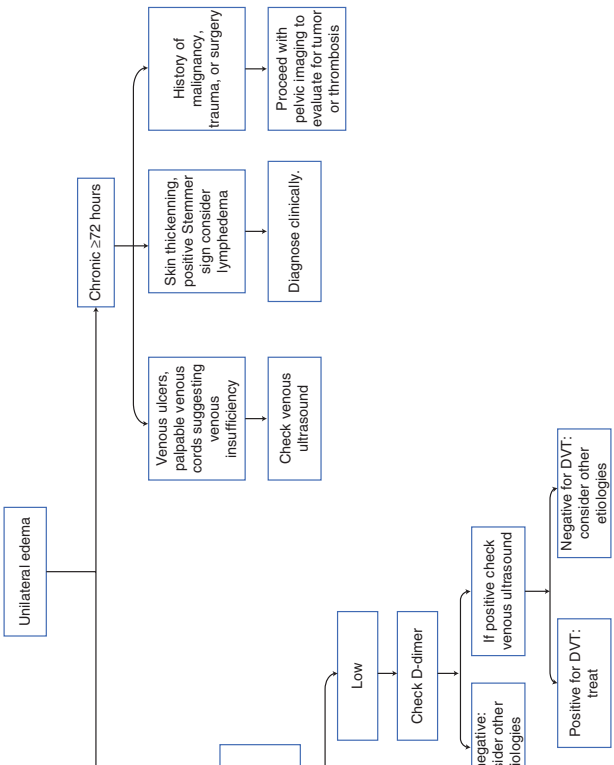

FIG. 18.3 Clinical approach for the patient presenting with unilateral edema

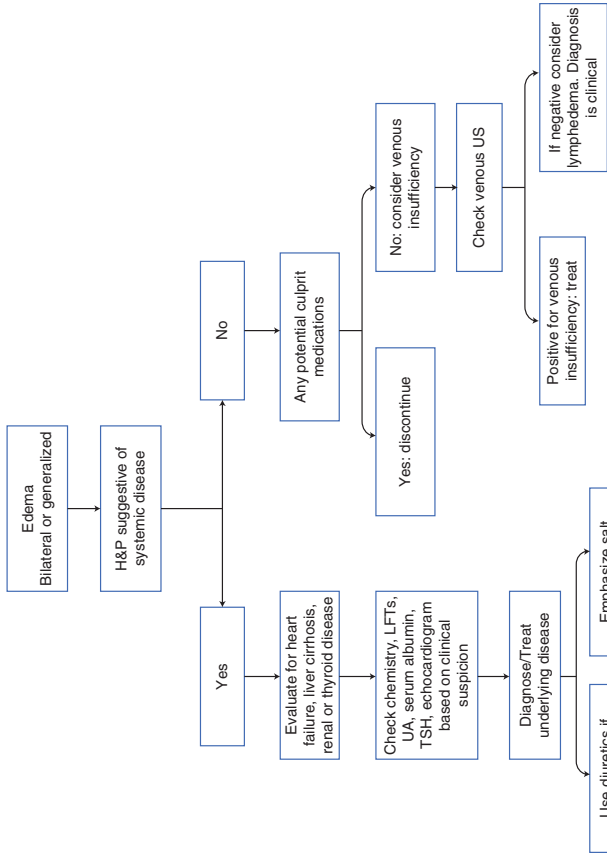

FIG. 18.4 Clinical approach for the patient presenting with bilateral or generalized edema

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.

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, 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 19
Rash

Alyssa Miceli and Karthik Krishnamurthy

Introduction

Rashes are common problems encountered in primary care offices, dermatology practices, and emergency rooms that often represent a diagnostic conundrum, even to the most experienced practitioner. Many conditions produce rashes that appear very similar clinically, and the differences distinguishing them are often subtle. It is important that the correct diagnosis be made initially. Many conditions can be exacerbated by incorrect treatments, and lack of prompt intervention can lead 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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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_19

Decision-Making/Differential Diagnosis

The initial step in approaching a rash is to create a detailed description of the rash. A good description includes shape, color, primary lesions, secondary changes, distribution, and configuration (see H & 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 angioedema, staphylococcal scalded skin syndrome (SSSS), toxic shock syndrome (TSS) , erythroderma, meningococcemia, etc.) [2].

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. 19.1).

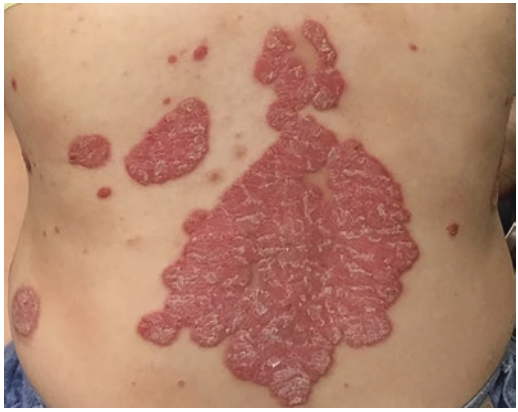

FIG. 19.1 Plaque psoriasis. Thick, red plaques with sharply demarcated borders and overlying silvery scale

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 [3].

Pityriasis rubra pilaris. Reddish-orange scaly plaques, keratotic follicular papules, 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 [3].

Pityriasiform

Pityriasis rosea. Oval-shaped pink to red scaly thin plaques in "Christmas tree" distribution along the body folds. 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 [3] (Fig. 19.2).

Erythroderma

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 [3] (Fig. 19.3).

Eczematous

1. *Acute eczema*. Weeping, vesicular erythematous papules and plaques that are very itchy. Geometric or linear configuration indicates "outside job" and is a clue to diagnosis [1]. Includes acute allergic/irritant contact dermatitis and dyshidrotic eczema.
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 patient cannot reach to scratch) will be spared (Fig. 19.4).

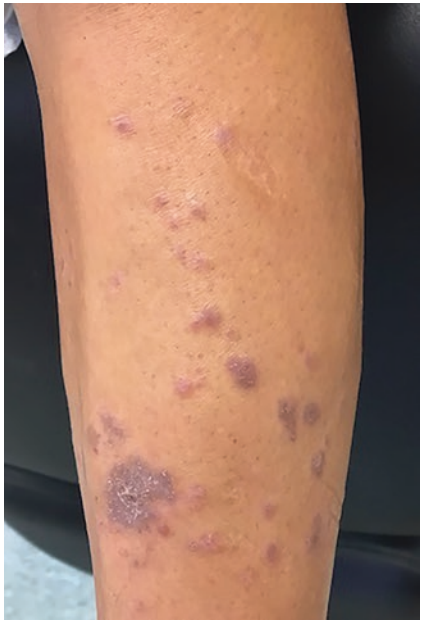

FIG. 19.2 Lichen planus. Purple, polygonal, planar plaques on the anterior lower extremity

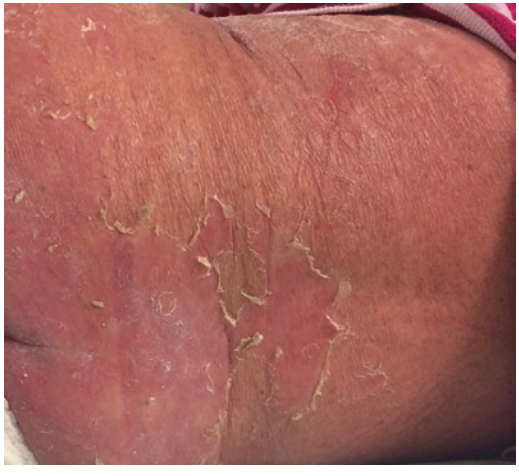

FIG. 19.3 Erythroderma, Generalized erythema and exfoliative scaling in a patient with underlying psoriasis

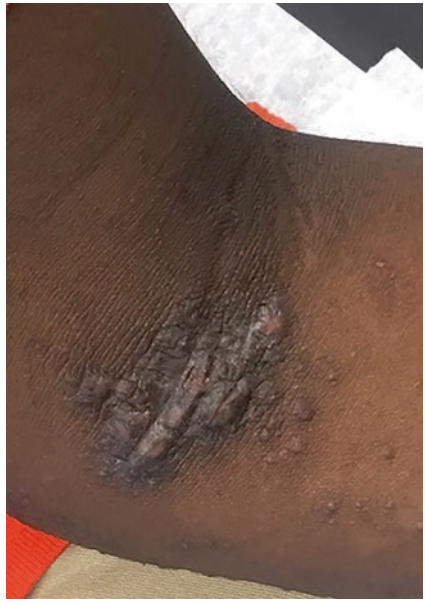

FIG. 19.4 Chronic eczema. Lichenification and hyperpigmented papulonodules in the antecubital fossa of a child with atopic dermatitis

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.

Dermal

1. *Subcutaneous*
   Panniculitis. Erythematous deep nodules:
   (a) *Septal*: superficial thrombophlebitis, erythema nodosum, or cutaneous polyarteritis nodosa
   (b) *Lobular*: erythema induratum, Crohn's disease, calciphylaxis, lupus panniculitis, or pancreatic panniculitis (Fig. 19.5)

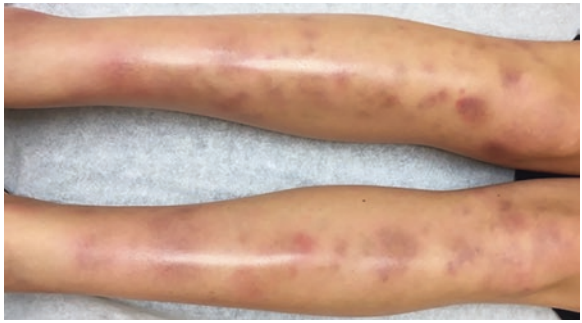

FIG. 19.5 Erythema nodosum. Tender, erythematous nodules over the shins in a young female taking oral contraceptive pills

Cellulitis. Erythema, edema, warmth and pain with/without fever, and lymphadenopathy

2. *Inflammatory*

   Lupus erythematosus. Malar erythema (spares nasolabial fold) with confluent erythema and edema or maculopapular lesions in sun-exposed areas. Oral ulcers may be present.

   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.

   Sarcoidosis. Purple-red or brown indurated circular plaques. Erythema nodosum may be present.

3. *Infectious*

   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.

   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.

   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- to 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, conjunctivitis. Treat with clindamycin, vancomycin, or nafcillin.
(d) *Kawasaki disease.* Polymorphous rash, strawberry tongue, conjunctivitis, redness and scaling of palms and soles, cervical adenopathy. Treat with aspirin and IVIG [4].
(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 [5] (Fig. 19.6).

(a) *Hypersensitivity*. Symmetric. Infection (HCV, group A *Streptococcus* (GAS), autoimmune disease, drug, malignancy, Henoch-Schonlein purpura.
(b) *Septic*: Asymmetric, often involving acral surfaces. Meningococcemia, pseudomonas, gonococcemia, GAS.

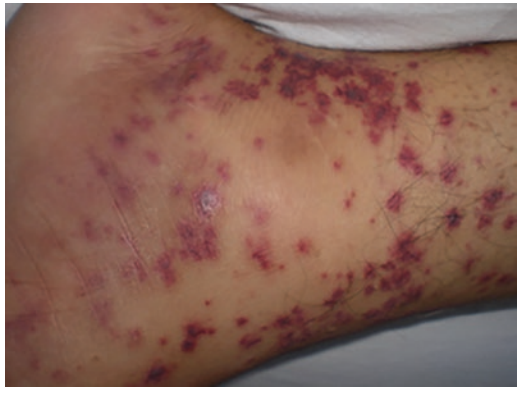

FIG. 19.6 Palpable purpura on the lower extremity indicating leukocytoclastic vasculitis

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) [5].
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 [6].

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. 19.7).

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.

Autoimmune, Intraepidermal

Pemphigus vulgaris (*PV*). Flaccid blisters with crust and erosions present. Oral involvement is common. Positive Nikolsky sign.

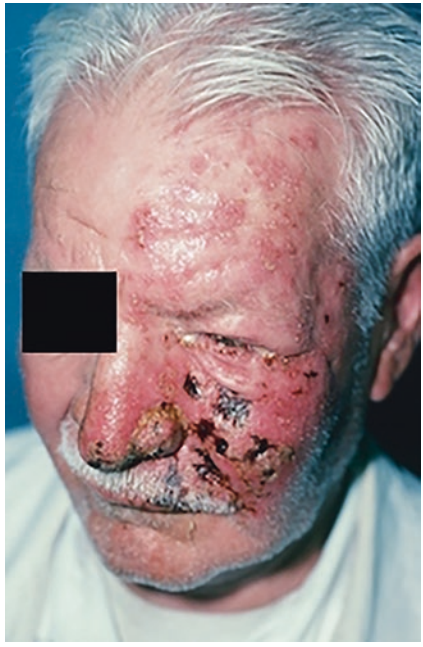

FIG. 19.7 Herpes zoster. Vesicles and crusting involving the trigeminal nerve (V1 and V2) distribution

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. 19.8).

Noninflammatory

Porphyria cutanea tarda. Acral blisters that worsen with sun exposure, alcohol use, and estrogen [7].

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.

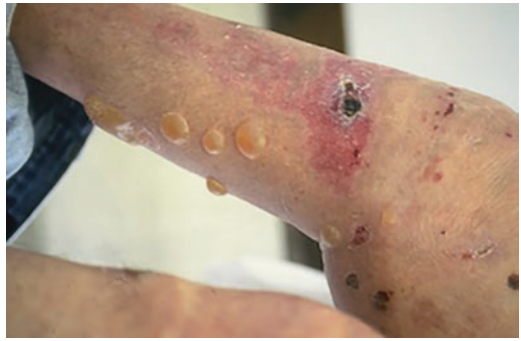

Fig. 19.8 Bullous pemphigoid. Tense bullae on the lower extremities. Previously published in Buka B, Uliasz A, Krishnamurthy K. Buka's Emergencies in Dermatology. New York: Springer; 2013

History and Physical Examination

History:

- Duration of rash: acute vs. chronic
- Description: location of rash, color, texture, symptoms (itchy, painful, changes in color or texture, drainage, fever)
- 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 [8]:
  - *Shape:* Annular, round, ovoid, linear, serpiginous, targetoid, polycyclic (overlapping annular), arcuate (incomplete annular), polymorphous (many shapes)

- *Color*: erythematous, hyperpigmented/hypopigmented, flesh-colored, red-brown, violaceous, purpuric, dusky (dark purple/gray that suggests necrosis)
- *Primary skin lesions*: macules, patches, papules, plaques, nodules, vesicles, bullae, pustules, hives or urticaria, petechiae, purpura, furuncle, carbuncle
- *Secondary skin changes*: excoriations, scale, crust, erosions, ulcerations, fissures, lichenification
- *Distribution*: generalized, central, peripheral, palms/soles involved, flexural vs. extensor surfaces, unilateral vs. symmetric, sun-exposed areas, intertriginous, mucosal involvement
- *Configuration*: linear/geometric (suggests outside influence), dermatomal, grouped
- *Texture*: soft, firm, fleshy, indurated
- *Patterns*: follicular, morbilliform ("measles like" a.k.a. maculopapular), reticular ("net like"), monomorphic, guttate (drop like)

- Diagnostic procedures:
  - 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].
  - Scabies prep: Identifies scabies.
  - Positive test: Observe mite, eggs, or feces (scybala). Mineral oil used.
  - Wood's lamp (365 nm) [3]:
  - 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 on blister causes easy rupture of blister. This 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.
  - 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).

- Treatment: Please see diagnostic and treatment Figs. 19.9, 19.10, 19.11, 19.12, 19.13, and 19.14.

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.
- Punch biopsies (3–5 mm) should be used for nonresponding or undiagnosed rashes, and a DIF should be performed for vesiculobullous eruptions.

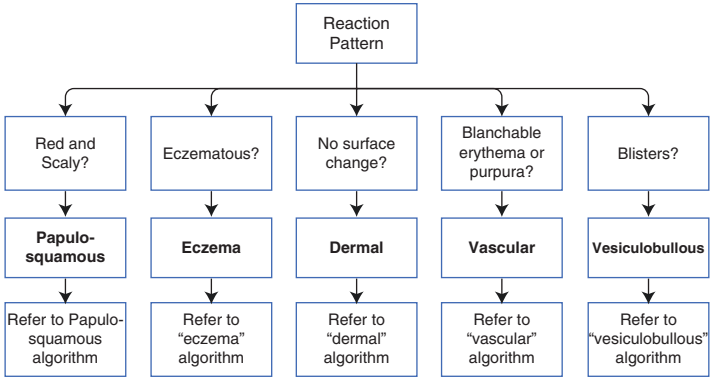

Fig. 19.9 Approach to rashes based on clinical reaction patterns

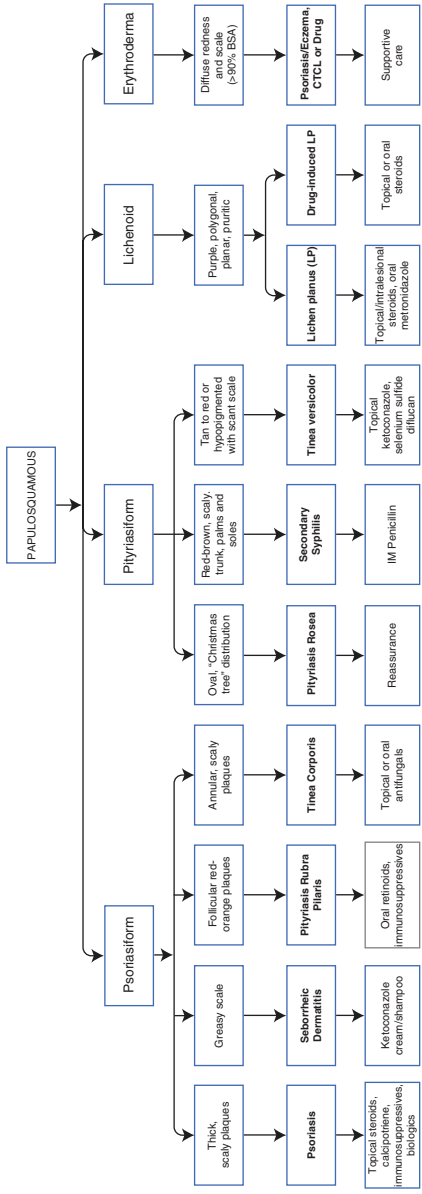

FIG. 19.10 Algorithm for rashes with papulosquamous reaction patterns

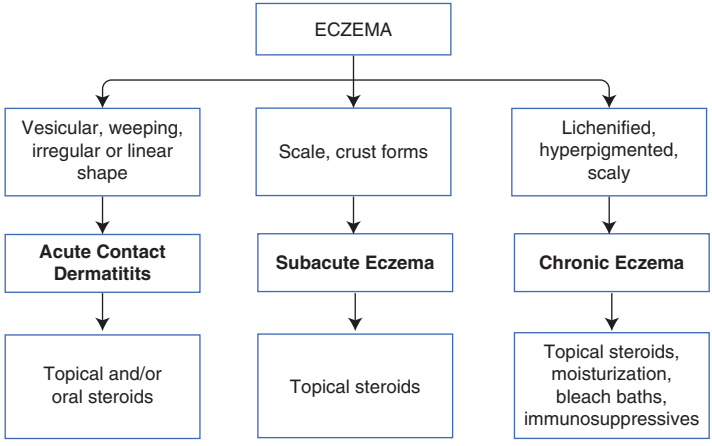

FIG. 19.11 Algorithm for rashes with eczematous reaction patterns

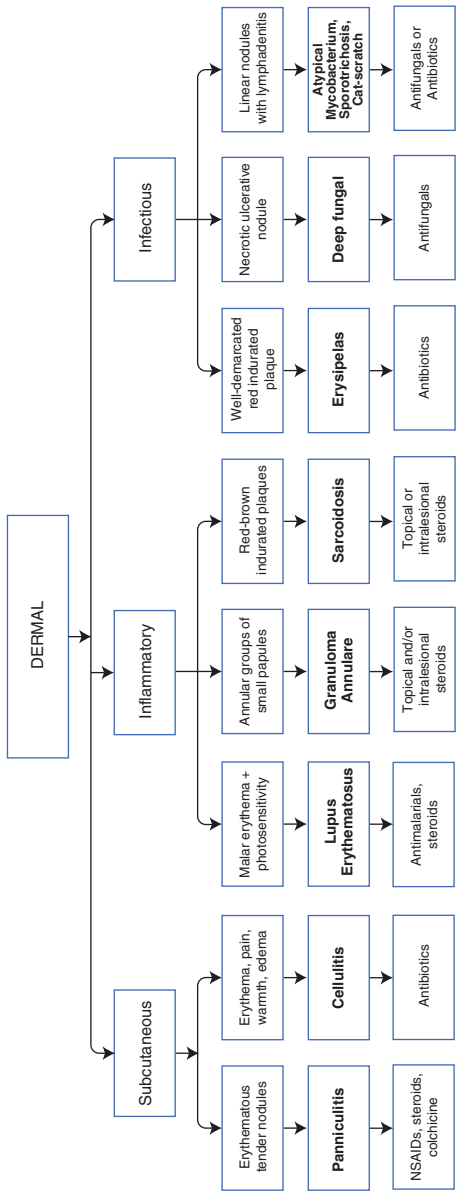

FIG. 19.12 Algorithm for rashes with dermal reaction patterns

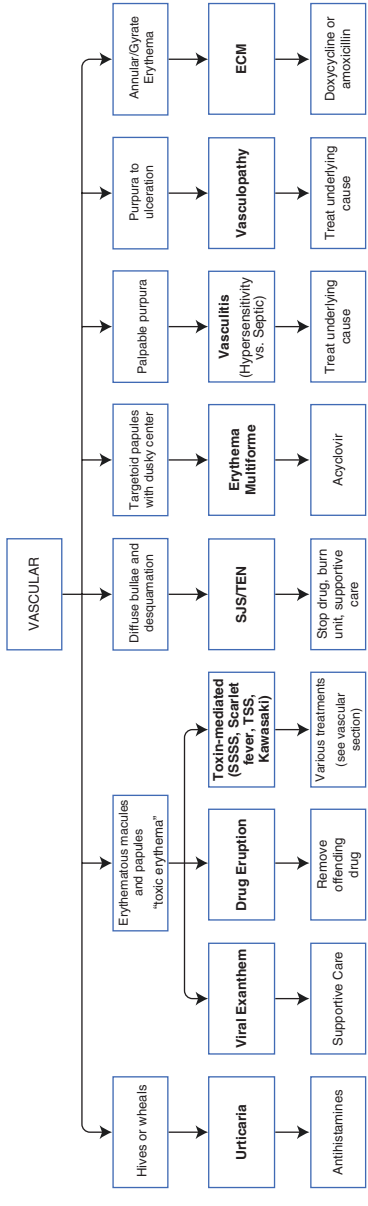

FIG. 19.13 Algorithm for rashes with vascular reaction patterns

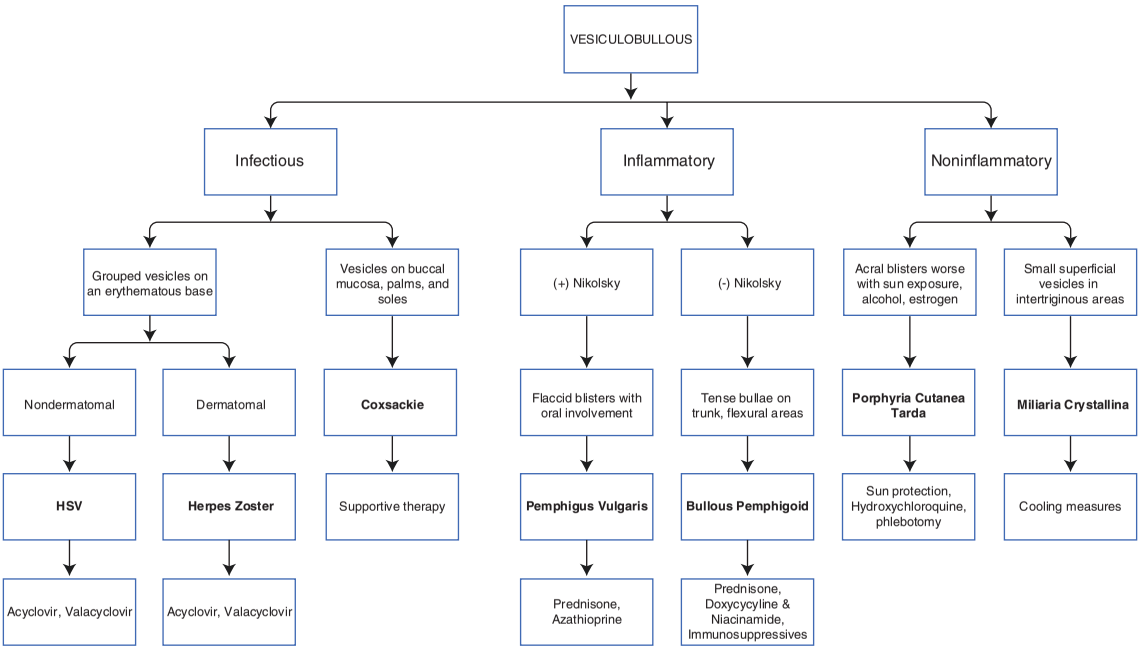

FIG. 19.14 Algorithm for rashes with vesiculobullous reaction patterns

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Chapter 20
Hair Loss

Alyssa Miceli 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.

A good understanding of the normal hair life cycle is important when approaching alopecias. There are three main phases of the hair follicle 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].

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_20

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. The alopecias are divided into two main categories: scarring (or cicatricial) and non-scarring (or non-cicatricial) alopecias (Fig. 20.1). Female and male pattern hair loss, or what most people refer to as "balding," is the most common type of hair loss. 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.

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

Pattern (Androgenetic)

Androgenetic Alopecia. 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 can begin any time after puberty, when androgens begin to be synthesized [2, 3].

Features:

- Gradual thinning without noticeable shedding.
- Strong genetic disposition, with a high concordance amongst monozygotic twins.

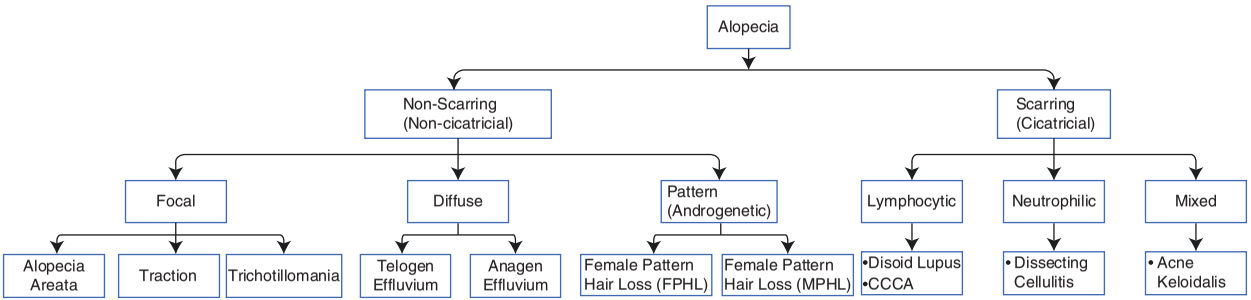

FIG. 20.1 Hair loss algorithm

- Male pattern hair loss: symmetric and progressive, typically affecting the frontoparietal area with frontal recession as well as vertex thinning.
- 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.

Focal Hair Loss

Alopecia Areata. This is usually a hair-specific autoimmune phenomenon in which T-cells interact with follicular antigens. Alopecia areata can be associated with other autoimmune diseases, including Hashimoto's thyroiditis, vitiligo, inflammatory bowel disease, and type I diabetes [4].

Characterized by:

- Discrete circular patches of hair loss.
- Loss of all scalp hair (alopecia totalis) or all scalp and body hair (alopecia universalis) can occur.
- Ophiasis pattern: band-like pattern of hair loss that occurs along the periphery of the temporal and occipital scalp.

Traction Alopecia. Occurs due to physical stress on the hair follicle secondary to tight hairstyles, including ponytails, braids, and hair weaves:

- Occurs along the outer hairline, typically in the frontal and temporal areas
- 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]:

- Often begins in childhood.
- More common in females than males.

- Patients may pull hairs out from other hair-bearing areas such as the eyebrows, eyelashes, face, extremities, and pubic area.

Diffuse Hair Loss

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.
- Causes include: severe infections, postsurgical, postpartum, hypothyroidism, anemia, malnutrition, and drugs (especially beta-blockers) [5].
- In many instances, a discernable precipitating cause cannot be found.

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 [6].

Lymphocytic

Central centrifugal cicatricial alopecia (CCCA):

- A chronic, progressive disease that is centered on the crown or vertex.
- Expands peripherally in a symmetric fashion.
- It is found almost exclusively in African Americans.

Discoid lupus erythematosus. A form of cutaneous lupus erythematosus that occurs most commonly on the face, ears, and scalp:

- 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.

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]"

1 Group of disorders in which the hair follicle becomes blocked with keratin, including hidradenitis suppurativa, acne conglobata, and dissecting cellulitis.

- It most often affects young adult black men.
- Over time, the nodules become boggy, fluctuant, and interconnected and will discharge purulent material.

Key History and Physical Exam

Various diagnostic tools can help differentiate types of alopecia. A detailed history and physical 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
- Telog39en 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 20.1) [1–6]

General Measures

- Treat underlying medical problems: thyroid disorder, iron deficiency.
- Discontinue any possible contributing medications, especially in telogen effluvium.

TABLE 20.1 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
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

(continued)

Table 20.1 (continued)

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

- Advise patient of importance of changing hair practices: traction alopecia, 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
Orthopedic

Chapter 21
Knee Pain

Mitsuyo Kinjo

Introduction

The knee has 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 History and Physical Exam

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 activity, ask if the knee pain occurs with activity. The patient

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_21

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 (<6 weeks) or chronic (>6 weeks). Pertinent historical questions include the following.

- Did pain develop following an injury or increasing activity level?
- Did you twist the knee while your knee was flexed? (meniscus tear)
- Is the pain exacerbated by activity? Does the knee feel stiff?
- Which activity worsens the pain: while walking on uneven surface, walking up and down stairs, flexing the knee, or pivoting? (ligaments or meniscus tear)
- Where is the pain located (anterior, lateral, medial, or posterior)?
- Is the knee pain bilateral?
- Do you feel the knee is getting locked in place? Does the knee give way during walking or climbing stairs without pain?
- Are there any symptoms or signs of systemic illness? Are there any fever, chills, night sweats, weight loss, fatigue, or rash?
- Was the knee pain associated with swelling? Is there any other joint pain or swelling?

Knowing the details of the traumatic event is helpful. If the knee is twisted while in a flexed position, meniscus tear is suggested [2]. 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 degenerative osteoarthritis tends to be accompanied by stiffness

and is worse with exercise or activity. Knee pain of osteoarthritis (OA) can be anteromedial or more generalized on the medial side of the tibiofemoral joint, or anterior in the patellofemoral joint [4]. Joint swelling following trauma indicates bleeding or ligamentous/ meniscus injury. Knee swelling unrelated to trauma may suggest infection, inflammation secondary to crystal or rheumatic diseases. Bilateral knee pain suggests osteoarthritis or rheumatoid arthritis. Unilateral pain is often due to injury, meniscus tear, septic arthritis, or crystal induced arthritis.

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 about any prior injury surgery to the lower extremities.

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 ambulatory assist device use and walking capability.

Physical Examination

The 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, assess gait, swelling, ecchymosis and other signs of injury, muscle atrophy, alignment, and skin changes.

Palpation of the knee includes skin temperature, medial and lateral joint lines, bursae, and the posterior knee. Joints are normally cooler than surrounding skin. If the patient can pinpoint localized pain, attention should be paid to specific structures in that location (Fig. 21.1). If there is tenderness over the medial anterior aspect of the tibia below the knee, pes anserine bursitis is suggested [5]. Diffuse tenderness along the joint line is often caused by degenerative, inflammatory, or infectious pathology. 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 expressing it with examiner's finger (causing a fluid wave) can identify an effusion.

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.

Vascular assessment includes palpating the lower extremity pulses of the dorsalis pedis, posterior tibial, and popliteal arteries.

Knee pain can present as referred pain. 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. As a general rule, it is recommended to examine the contiguous joints.

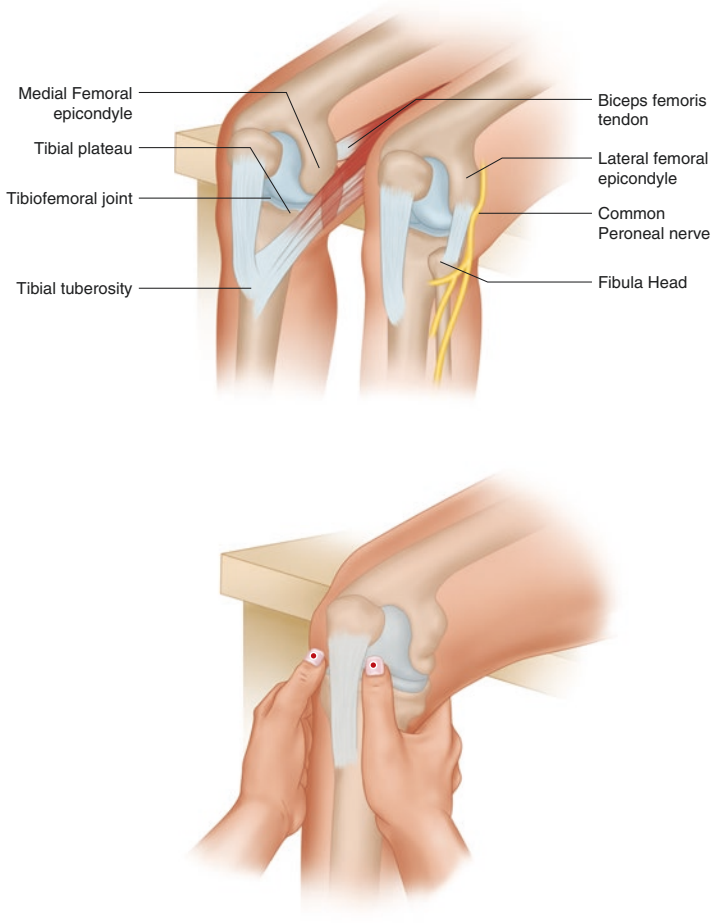

FIG. 21.1 Anterior knee

Provocative maneuvers are only tested when initial history and examination suggest specific conditions.

MCL (medial collateral ligament) valgus test is performed with the 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 the examiner applies 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 degrees of knee flexion, the capsule and cruciate ligaments provide no secondary restraints to valgus stress. Thus, a positive valgus test at 0 degree suggests injury to both the MCL and cruciate ligament, but a positive test at 30 degrees 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 (lateral collateral ligament) varus stress test, place one hand along the medial aspect of the knee joint and hold the ankle while applying varus force to the knee and 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 degrees, 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.

Patellofemoral pain is experienced with squatting. In the apprehension test, quadriceps are relaxed and the knee flexed to 30 °, then the examiner puts pressure to the patella from the medial side to laterally, 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 incorporates weight bearing 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 a locking/catching sensation during rotation of the knee considered a positive test.

Differential Diagnosis

See Fig. 21.2 for a visual representation of differential diagnoses.

Causes of acute knee pain following acute trauma or recent overuse:

- Medial or lateral collateral ligament tear—after medial or lateral force trauma
- Anterior/posterior cruciate ligament tear—after anterior or posterior force trauma
- Meniscus tear—twisting trauma
- Intra-articular fracture
- Patellar dislocation
- Patellar tendon tear

Knee Pain Associated with Activity

Diffuse Pain

- Knee osteoarthritis—progressive, long-standing pain. Commonly seen in overweight patients

Anterior Knee Pain

- Osgood-Schlatter disease—tibial tubercle pain seen mostly in growing children and teens
- Quadriceps and patellar tendinopathy—overuse injury seen in avid exercisers
- Bursitis (prepatellar and infrapatellar)—overuse, from working on knees (setting tile or scrubbing floors or praying)
- Patellofemoral pain—common in female distance runners

Medial Knee Pain

- Degenerative meniscal tear—chronic in presentation
- Saphenous nerve entrapment

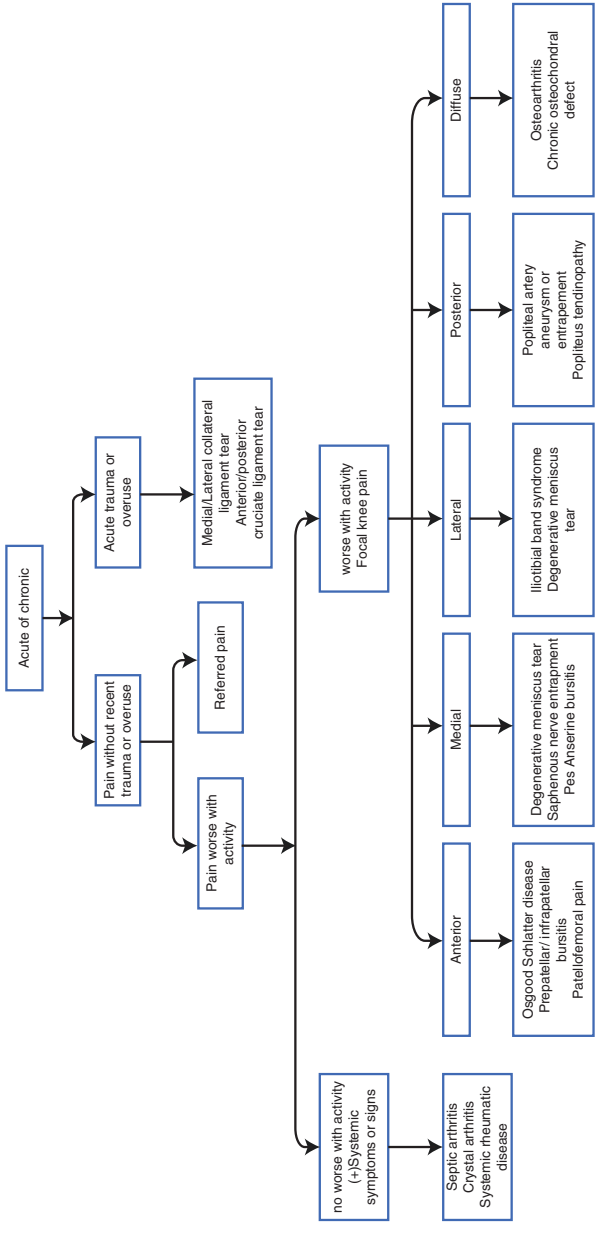

FIG. 21.2 Knee pain algorithm

- Pes anserine bursitis—distal to the joint

Lateral Knee Pain

- Iliotibial band syndrome—seen in runners, palpable at the joint or lateral thigh
- Degenerative meniscus tear

Posterior Knee Pain

- Popliteal artery aneurysm or entrapment
- Popliteus tendinopathy
- Popliteal (Baker's) cyst—non-pulsatile fullness, may mimic deep vein thrombosis

Acute knee pain with intense inflammation, onset not associated with activity:

- Septic arthritis
- Crystal arthritis
- Inflammatory arthritis (systemic rheumatic diseases)

Decision-Making

If the knee pain began following acute trauma, plain radiography 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. MRI should be considered for any patient with knee instability, or in other words, when the knee gives out and the patient falls.

If a patient reports systemic symptoms or signs when arthritis of the knee presents with local erythema, warmth, joint pain, 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 the knee pain is worse with activity but there is no inciting trauma, changing of the patient's exercise 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 on 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 muscle around the affected joints, which lead to improvement of pain and functional outcome. The guideline 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 tears without osteoarthritis, the use of physical therapy to strengthen quadriceps muscle and lower extremity function is recommended.

Referral to an orthopedic surgeon is needed for MCL/LCL injury with the unstable knee suggesting multiple ligament involvement.

Clinical Pearls

- Knee pain could be referred from the lower back or hips.
- Septic arthritis could present with absence of fever, normal CBC, or unremarkable erythrocyte sedimentation rate.
- Simple maneuvers (drawer, McMurray, valgus, and varus tests) can isolate the source of an injury.

Don't Miss This!

- The presence of crystals in the joint fluid analysis does not exclude concurrent septic arthritis.
- Examine the joint above and below the knee to identify referred pain.

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Chapter 22
Shoulder Pain

Mitsuyo Kinjo

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.

The shoulder girdle is composed of three bones (clavicle, scapula, and humerus) and four articular structures (sternoclavicular, acromioclavicular, glenohumeral, and scapulothoracic joints) (Fig. 22.1). 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 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.

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_22

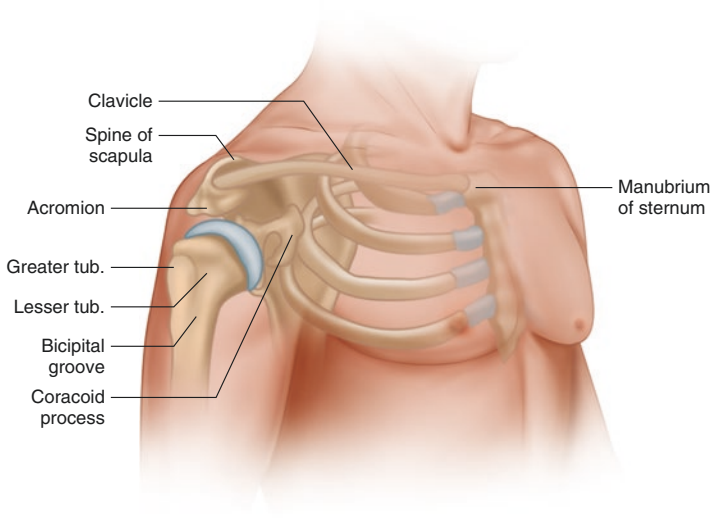

FIG. 22.1 Anterior shoulder. Modified from Kinjo M, Kinjo K, et al.: Manual of Clinical Procedures in Outpatient Internal Medicine, 2nd. ed. Tokyo, Igaku-Shoin Ltd. 2017

Key History and Physical Exam

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, and 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. The patient is asked to point to the specific site of the pain, such as the acromioclavicular joint, biceps tendon, or scapula. 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 arm laterally in an arc). In biceps tendinopathy, shoulder pain is often felt in the anterior aspect of the shoulder with tenderness in the bicipital groove. 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 immobility 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 impingement is suspected when patients complain of subacute lateral shoulder pain worse with movement overhead. Rotator cuff tear is often of sudden onset associated with weakness and pain at night [3]. Inflammatory polyarthritis involving 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. History elements for Shoulder pain

- 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?
- 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 biceps hurt when lifting or carrying heavy objects?
- Is the shoulder pain at rest and is it worse in the morning?
- Is there presence of fever, weight loss, dyspnea, or chest pain?

Physical Examination

First, compare 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 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.

When palpating the shoulder and surrounding pathology, the cervical spine is first to be examined, then moving 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.

Full range of motion suggests a normal glenohumeral joint, rotator cuff tendon, 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. 22.2). Finally, ask the patient to reach across the chest and touch the opposite shoulder to assess adduction.

Diminished both active and passitve ROM in all direction indicates either adhesive capsulitis or glenohumeral arthritis. If active ROM is diminished but passive ROM is normal, differential diagnosis includes rotator cuff disease, labral tear, biceps tendinitis, or AC joint osteoarthritis. Provocative maneuvers for examination of rotator cuff injury are impor-

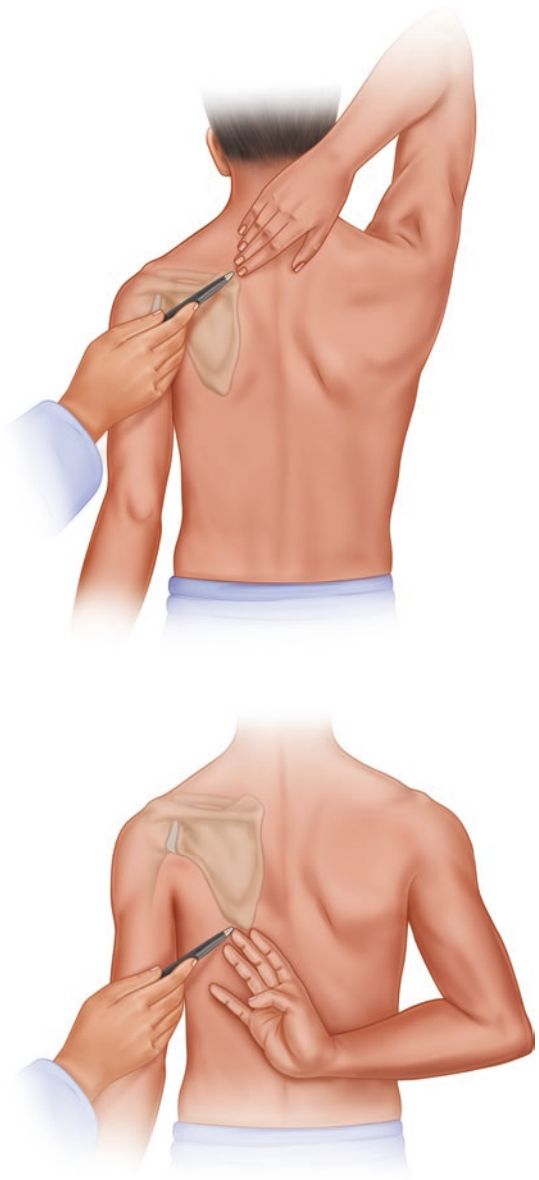

FIG. 22.2 Apley scratch test. Modified from Kinjo M, Kinjo K, et al.: Manual of Clinical Procedures in Outpatient Internal Medicine, 2nd. ed. Tokyo, Igaku-Shoin Ltd. 2017

tant. Rotator cuff disease includes impingement, tendinitis, partial thickness tear and full thickness tear. 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 having 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 scapular plane (Fig. 22.3). 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 subacromial impingement (supraspinatus tendinopathy or subacromial bursitis) [3]. Pain between 120 and 180° suggests problems in the acromioclavicular joint. Provocative maneuvers for full thickness rotator cuff tear are external rotation lag test and internal rotation lag test, which are important because this condition requires surgical intervention. In external rotation lag test when patient abduct shoulder 20 degrees and flex elbow 90 degrees, examiner passively rotate patient arm into full external rotation. If the patient is unable to maintain the position of full external rotation, the test is considered positive. In internal rotation lag test, if patient is unable to maintain the position when the hand of patient is lifted off from the back by examiner, the strength of subscapularis muscle is diminished by the tear [3].

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. 22.4). In this test, the patient 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.

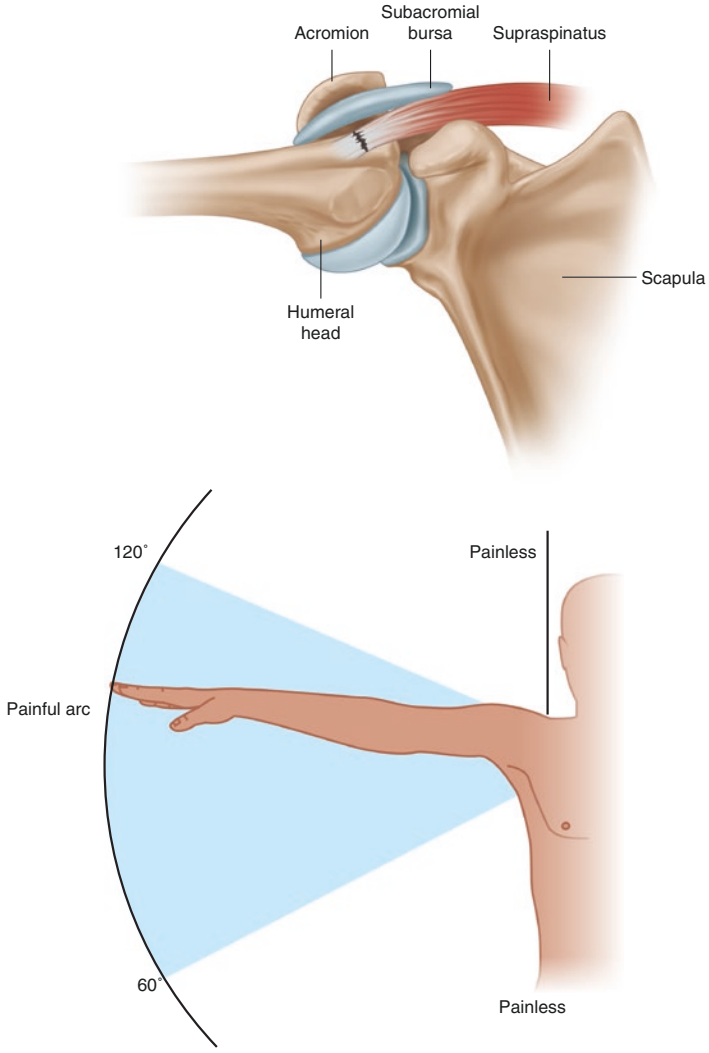

FIG. 22.3 Impingement sign. Modified from Kinjo M, Kinjo K, et al.: Manual of Clinical Procedures in Outpatient Internal Medicine, 2nd. ed. Tokyo, Igaku-Shoin Ltd. 2017

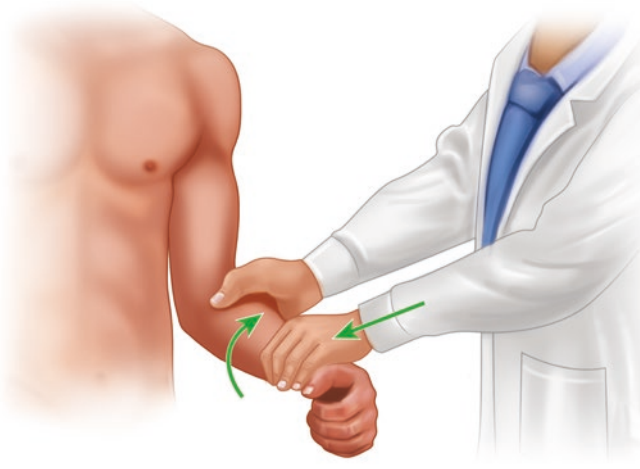

FIG. 22.4 Yergason's test (bicipital tendinitis). Modified from Kinjo M, Kinjo K, et al.: Manual of Clinical Procedures in Outpatient Internal Medicine, 2nd. ed. Tokyo, Igaku-Shoin Ltd. 2017

Differential Diagnosis

Please see algorithm (Fig. 22.5) 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, 6)
- 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)

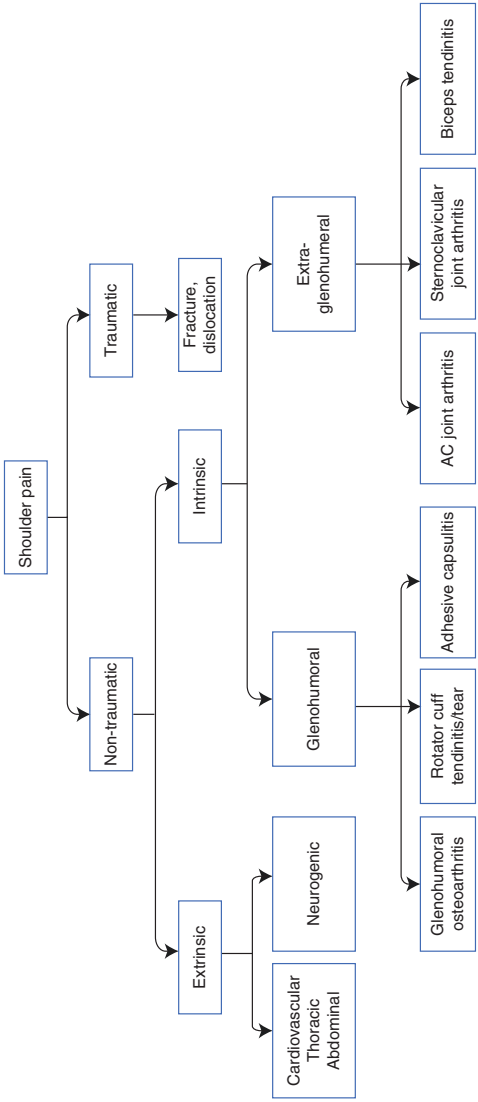

FIG. 22.5 Shoulder pain algorithm

Cardiovascular

- Myocardial ischemia

Thoracic

- Upper lobe pneumonia
- Apical lung tumor
- Pulmonary embolism

Intrinsic Shoulder Pain

Nonspecific shoulder pain

Polymyalgia rheumatica

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 or 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 especially full thickness rotator cuff tear, 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."

Patients unable to tolerate NSAIDs may respond to injection of steroids, as described under the adhesive capsulitis section below.

Rotator Cuff Injury

Suspected full thickness rotator cuff tear requires orthopedic referal. Other rotator cuff diseases often do well with conservative treatment. 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, 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, 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.

Don't 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. Don't forget to examine this area.
- When rotator cuff disease is considered, full thickness tear should not be missed as it requires specialist referral.

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Chapter 23
Back Pain

Mitsuyo Kinjo

Introduction

The majority of patients who present with back pain to a 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 the specific etiology of back pain. The history of back pain includes location, duration, and severity of the pain, activities, or detailed events prior to the onset of the back pain. In order to make sure not to miss a serious etiology, red flag signs and symptoms should be elicited.

Upper/middle back pain is located from the posterior neck to the lowest rib edge, and low back pain is located from the thoracolumbar spine down to the sacrum. Upper/middle back pain is often due to mechanical problems, whereas low back pain is related to various pathologies.

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_23

Key History and Physical Exam

First, ascertain if the back pain is acute/sudden or chronic. Patients with severe back pain with abrupt onset or abnormal vital signs should be seen in the emergency room.

Next, red flag signs reflecting underlying systemic illness or an 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. Key historical features include 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 invasive procedures to the back.

Distribution of low back pain is either classified as axial (pain generally localized to the low back) or radicular neuropathic (pain radiating to the lower extremities). This classification often helps the primary care physician to identify disease processes 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. The 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 lumbar 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-S5 nerve roots) suggests cauda equina syndrome. Weakness of plantar flexion of the feet and loss of the ankle jerk reflex suggest S1-S2 nerve root involvement.

Numbness, cold, or burning sensations of the lower extremities are common symptoms of nerve root compression. This rare but serious condition usually arises from 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 fractures commonly affect 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, the 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, as usually is the case, the 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 pain in the paraspinal musculature.

Intervertebral disc herniation tends to occur in patients younger than 45 years old, and its onset is usually insidious but may have an inciting event such as lifting or bending. Patients will often report localized pain to the midline of the spine [5].

Herniated intervertebral discs at the L4-L5 or L5-S1 level are also an important cause of radicular pain. Clinicians should determine the distribution of the pain, which should follow one or multiple dermatomal patterns and is worsened by forward bending, coughing, and sneezing and improved with recumbency.

Lumbar facet joint hypertrophy frequently occurs in patients over 65 years old. Low back pain may be localized to the paraspinal region and is worse with standing and better with sitting or recumbency [5]. Sacroiliac joint pain is usually reported as pain in the paraspinal region below L5 or gluteal pain radiating to the thigh or distal to the knee and is worsened by transitional movements such as rising from the seated position.

The 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 this from radicular pain. Lumbar spinal stenosis could present with both axial and radicular pain. Patients older than 65 should be asked about neurogenic claudication, in which the pain worsens when standing and walking and improves when sitting or bending forward. Bilateral buttock or leg pain can also be present [7].

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. A specific underlying pathology or condition cannot be identified for the vast majority of patients. In most patients with nonspecific back pain, symptoms improve 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. A high index of suspicion is the key for the diagnosis especially for those with risk factors such as diabetes, alcoholism, hemodialysis, IV drug use, HIV, or spinal surgery/epidural catheter. History of cancer and severe back pain at rest suggest a metastatic skeletal lesion. Breast, prostate, lung, thyroid, kidney, and gastrointestinal tract cancers have a propensity for skeletal metastasis.

Neoplastic epidural spinal cord compression arises most commonly in the thoracic spine (60%), followed by the lumbar spine (30%) and cervical spine (10%). Previous spinal surgeries, history of osteoporosis, or prior fractures should be noted.

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 are associated with a higher prevalence of low back pain compared to those with sedentary occupations [9]. Lower educational status and obesity are also related to an increased risk of low back pain [10].

History Elements for Back Pain

- 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 previous back pain?

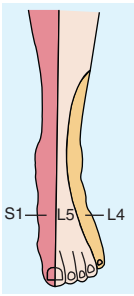
- Do you have prior history of cancer? If so, how long ago was it?
- Do you have fever or weight loss?
- Do you find it difficult to walk? Is there any numbness or change in sensation?
- Do you have any fecal/urinary incontinence?
- Do you have any recent preceding infection (bacterial pneumonia or urinary 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 worsened 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, straight leg raising test (elevation of the symptomatic leg to less than 60° with pain radiating below the knee is positive) and crossed straight leg raising test (elevation of the non-symptomatic leg to 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 in a dermatomal distribution are also helpful (Fig. 23.1). The L5 and S1 nerve roots are most commonly involved in lumbar disc herniation.

Lower extremity dermatomes, myotomes, and reflexes



Nerve Root	Sensory	Muscle	Tendon reflex
L2	Anterior medial thigh	Hip flexor	None
L3	Anterior thigh to knee	quadriceps	patellar
L4	Medial calf/ankle	Anterior tibialis	Patellar
L5	Lateral ankle/ dorsum of foot	Extensor hallicus longus	None
S1	Plantar lateral foot	Gastrocnemius/ soleus/ peroneals	Achilles

FIG. 23.1 Lower extremity dermatomes, myotomes, and reflexes

In lumbar spinal stenosis, motor or sensory findings mostly reflect the involvement of proprioceptive fibers in the posterior columns of the spinal cord [12]. Romberg sign and wide-based gait have moderate sensitivity but high specificity. Lumbar spinal pain is diminished on lumbar flexion, and vibratory and pinprick sensation are reduced. Achilles tendon reflex is often absent [13].

Sacroiliac joint pain is likely if it is reproduced by three or more of the following on physical examination: compression of the iliac crest in the lateral position, downward pressure on the anterior superior iliac crest, FABER test (flexion, abduction, and external rotation of the thigh and hip), Gaenslen test (hyperextension of the leg on the affected side), and Fortin finger test (pain localized within a finger breadth of the posterior iliac crest) [14].

Differential Diagnosis

- See Fig. 23.2 for a visual depiction of the differential diagnosis.

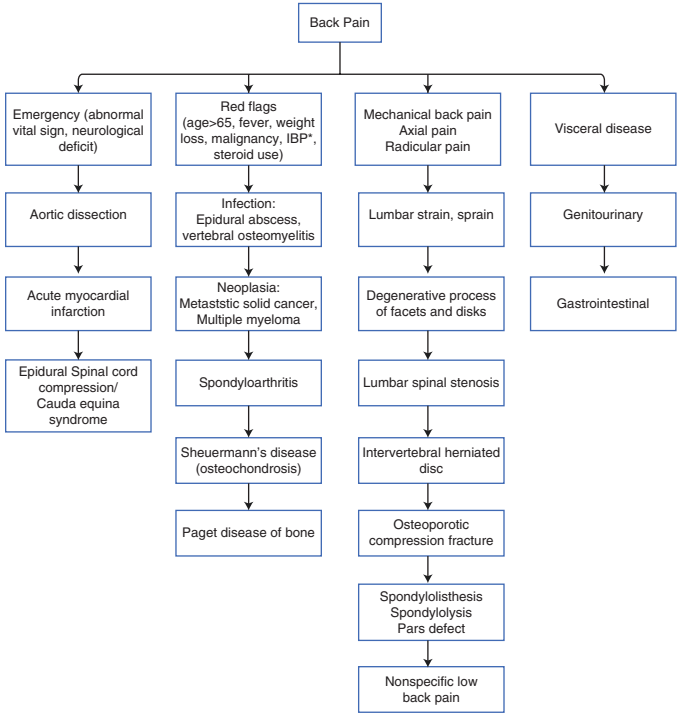


FIG. 23.2 Back pain algorithm

Serious Conditions

- Aortic dissection
- Acute myocardial infarction
- Anterior spinal artery syndrome
- Epidural spinal cord compression
- Cauda equina syndrome: trauma, tumors and metastatic lesions, and spinal stenosis
- Inflammatory diseases (e.g., spondyloarthritis), infectious conditions (e.g., tuberculosis)
- 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. Early imaging of axial low back pain or radiculopathy should be deferred until after initial treatment in the patient with weak risk factors for cancer or vertebral compression fracture. No imaging is indicated when back pain has improved or resolved 1 month after treatment [15].

Immediate imaging by MRI is indicated in the setting of progressive motor weakness, new urinary retention, or saddle anesthesia suggesting cauda equina syndrome. If current or recent cancer history and high clinical suspicion for malignancy is present, either MRI or plain X-ray should be performed. Spinal infection (epidural abscess or osteomyelitis) is strongly suspected in patients with risk factors including history of IVDU, recent infection, hemodialysis, or use of immunosuppressive agents. In this setting MRI and inflammatory markers such as ESR or CRP need to be checked. When infection is suspected, if blood cultures are positive for a likely pathogen (e.g., *Staph. aureus*), biopsy of the infected vertebral bone or intervertebral disc may not be necessary.

Vertebral compression fracture is suspected with advanced age, trauma, history of prolonged glucocorticoid use, and prior osteoporotic fracture. Plain X-ray film should be performed. Compression fracture with hypercalcemia, anemia, or elevated creatinine at presentation is suspicious for multiple myeloma. Monoclonal (M) protein can be detected by protein electrophoresis of the serum (SPEP) and/or of urine

(UPEP) from a 24-hour collection along with immunofixation of the serum and urine.

When spondyloarthritis is suspected, HLA-B27 positivity and MRI of sacroiliac joints help diagnose this condition.

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) for up to 3 months for chronic axial low back pain; however, short-term treatment within 4 weeks' duration is preferred. Start with 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 contraindications to NSAIDs should be advised to use acetaminophen.

Non-benzodiazepine muscle relaxants may be effective for patients with acute low back pain who are refractory to initial pharmacotherapy [17]. Cyclobenzaprine is a reasonable choice. Benzodiazepine muscle relaxants should not be used because of the risk of physical dependence. Tramadol may be effective for acute and chronic low back pain [18]. For radicular pain, gabapentin could be used as add-on analgesic 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. Encourage patients to return 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 muscles 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

- Osteoporotic compression fracture can mask malignancy-related vertebral compression fracture. Always look for any sign of malignancy or infection even when the history is highly suggestive of osteoporotic fracture.
- Most back pain seen in the clinic will be from a simple, mechanical cause.
- Patients with simple back pain should resume their usual activity and avoid bed rest.

Don't Miss This!

- Cauda equina syndrome secondary to malignancy or midline intervertebral disc herniation should not be missed as it could lead to irreversible neurological deficits.
- Aortic dissection and anterior spinal artery infarction are life-threatening conditions in the differential diagnosis of acute back pain in older patients.

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Part VII
Neurologic

Chapter 24
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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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_24

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. 24.1).

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

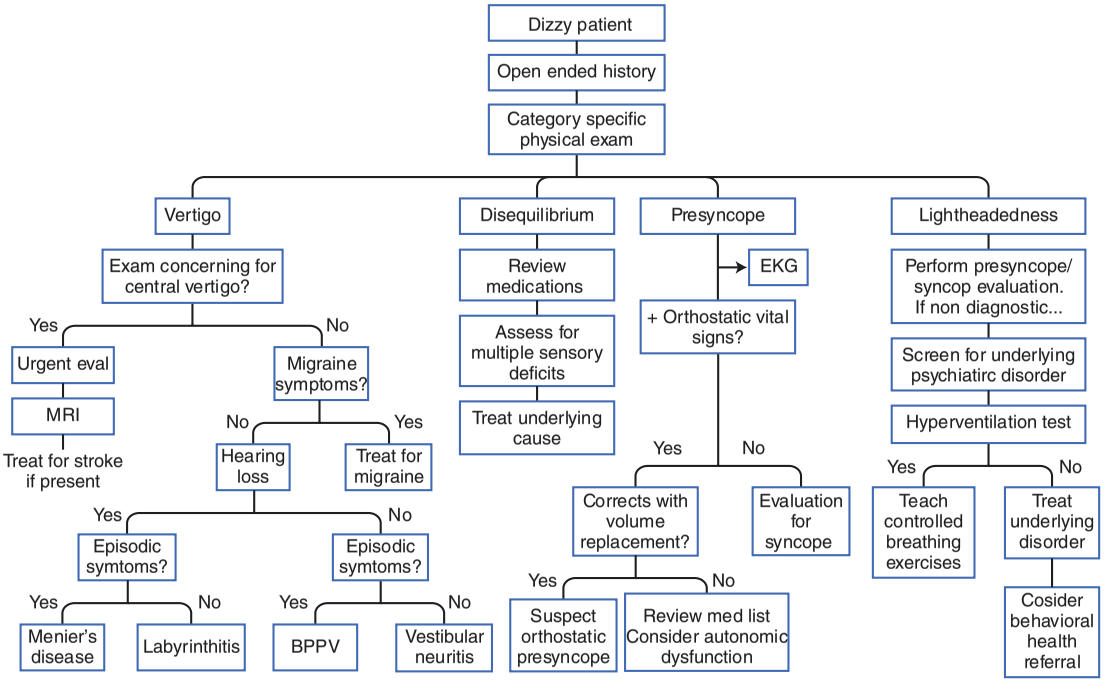

FIG. 24.1 Approach to patient with dizziness

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

Table 24.1 Finding 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

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, 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 24.1) [5].

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 supports 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

experienced 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, 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 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 don't 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 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, 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 system 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 abnormalities, 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 24.2).

TABLE 24.2 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. Non-invasive 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 underlying 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 experienced 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.

Don't 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 25
Headache

Schantal Polanco

Introduction

Headache is a common neurological complaint in the outpatient setting [1]. The importance of a proper diagnosis is crucial for appropriate 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 more 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 have 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 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

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_25

physical examination are excluded, one can focus on the more common primary etiologies of headache (Fig. 25.1).

Key History and Physical Exam

A complete history and physical examination is an essential part of 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.

History

Age: New headache in a patient above 50 should raise concerns for giant cell arteritis (GCA), acute angle closure glaucoma, and malignancy in the right context [1, 4, 5], 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 warrant immediate attention with imaging and lumbar puncture when imaging is non-revealing and our clinical suspicion is high. Etiologies which may present this way include subarachnoid hemorrhage (SAH), cavernous venous thrombosis (CVT), 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 work-up of secondary causes.

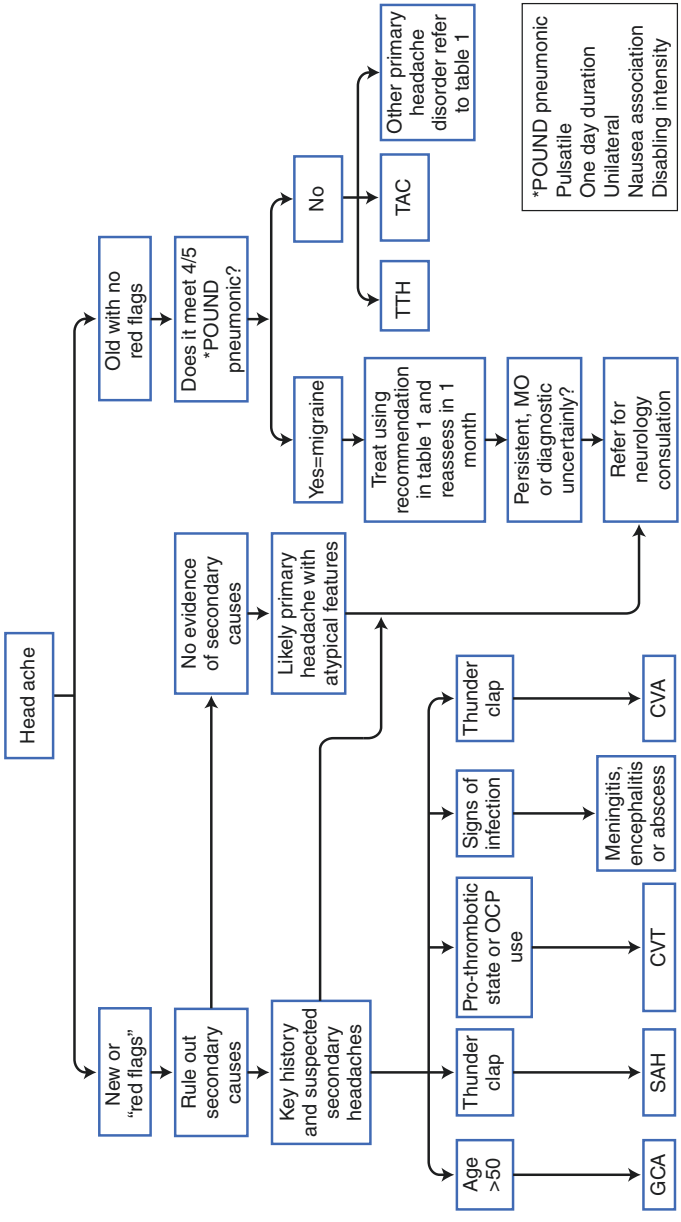

FIG. 25.1 Headache algorithm

Medications: Use of anticoagulants, NSAIDs, steroids, or drugs of abuse such as cocaine places 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 increases risk of CVT [6, 7].

Context: Headache in the setting of trauma, uncontrolled hypertension, and motor, sensory, cerebellar, personality, or cognitive change warrants imaging to further investigate the neurological symptom.
Aggravating factors that raise intracranial pressure such as exertion, coughing, or 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, temporomandibular joint (TMJ), ears, occipital nerve, and upper posterior neck can reveal pain stemming from various secondary headaches and neuralgias [5].

Physical Examination

Relevant vital signs: Hypertension and obesity can point toward a secondary diagnosis of hypertensive encephalopathy, pseudotumor cerebri, 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: Over maxillary and frontal sinuses, the orbits, temporal artery, TMJ, 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 similar pattern lasting 60 min or less) necessitates further investigation, such as neuroimaging to rule out mass lesion and serologic testing to rule out collagen vascular disease [4, 5].

Once 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 [8, 9]. 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 [10]. The five criteria most predictive of migraine can be remembered by the POUND mnemonic (pulsatile quality, 1-day duration, unilateral, nausea, or vomiting with disabling intensity) [11]. Patients meeting 4/5 of the POUND criteria have a greater than 90% chance of a having a migraine headache [11]. Further evaluation and diagnosis of primary headache etiologies are outlined by the international headache society (refer to Table 25.1). Once an accurate history is obtained, primary headaches can be classified based on four main categories to aid management (Table 25.2).

Tension-type headache (TTH) is the most common primary headache disorder [12, 13]. 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 tends to be the most disabling leading patients to seek medical attention most frequently for this condition [12]. 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 [9]. Most neurological symptoms last 1 h but motor disturbances may last up to 72 h [9]. Any headache with an acute neurological manifestation warrants intracranial imaging, often times making the diagnosis of

Table 25.1 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 (non pulsatile) 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 1 of phonophobia or photophobia

Lasting 30 min to 7 days and not better accounted for by another International Classification of Headache Disorders, 3rd 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:
   (a) Unilateral location
   (b) Pulsating quality
   (c) Moderate or severe pain intensity
   (d) 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

(continued)

Table 25.1 (continued)

3. Trigeminal autonomic cephalalgias (TACs) which includes 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
- 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 cephalalgia)
   - Hypnic headache: only during sleep
   - New daily persistent headache

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 [9]. Chronic migraine warrants preventive treatment and a neurological consultation.

The least common type of primary headache disorders falls 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

TABLE 25.2 *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
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 cephalalgia) – 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

symptoms [14]. Cluster headaches last 15–180 min, paroxysmal hemicrania (also described as indomethacin-responsive headache) occurs several times a day and lasts 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 [14].

Once a primary headache disorder is diagnosed, treatment options can be explored (refer to Table 25.3). 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 [15, 16] which warrants a different treatment approach and a neurology consultation.

Clinical Pearls

- The initial assessment of headache requires a thorough 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

TABLE 25.3 Treatment of common primary headache disorders

Type	TTH	Migraine	Cluster	CDH attributed to MO-Medication Overuse
Treatment options	Aspirin, acetaminophen, NSAIDs, or combination of aspirin, Tylenol, and caffeine typically enough to provide relief. Frequent TTH responds best to above mentioned therapy in addition to therapy aimed at reducing stress, anxiety, and depression [17]. Muscle relaxation to reduce stress and muscular pain is also recommended [16].	Mild: NSAIDs +/− metoclopramide Refractory or severe: Triptan Ergotamine Frequent attacks (>5 days per month) need preventive treatment with beta blockers, amitriptyline, or antiepileptic such as valproic acid and topiramate [16, 17]	Oxygen Triptan Ergotamine, before anticipated attack. Persistent or frequent need for preventive treatment with short course of steroids plus verapamil, valproate, and/or lithium in refractory cases [16, 17].	Withdraw overused medication and allow headache to revert to episodic pattern [13] Behavioral therapy and acute treatment of primary headache disorder are recommended [15].

Adapted from references [15–17]

symptoms highlighting the need for reassessment once therapy is commenced.
- Persistent symptoms despite treatment warrant further work-up to rule out secondary causes and a formal neurology consult.

Don't Miss This!

Most headaches are of benign etiology, but secondary etiologies while rare can be life-threatening and must be ruled out. Trauma, age above 50, 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 26
Vaginal Discharge

Alejandra Sanchez Lopez

Introduction

Vaginitis is a common disorder that affects women in all age groups, and it is characterized by vaginal complaints such as pruritus, burning, irritation, odor, and vaginal discharge [1]. Vaginitis is frequently seen in primary care and is reportedly the most common reason for gynecological consultation [2].

Vaginitis may result from infectious and noninfectious causes. In the first category, the three most common disorders are bacterial vaginosis (BV), vulvovaginal candidiasis, and trichomoniasis, accounting for most of all infectious causes [3–5]. Other pathogens can be associated with vaginal complaints such as chlamydia, gonorrhea, and herpes; however these may mimic vaginitis as they affect primarily the endocervix. Noninfectious etiologies include postmenopausal atrophic vaginitis, allergic reactions, and contact dermatitis.

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_26

Bacterial Vaginosis

The vaginal flora is a microsystem composed of a diverse group of aerobic, facultative anaerobic, and obligate anaerobic species [6]. Among these bacteria, *Lactobacillus* spp. are thought to have a special role by producing hydrogen peroxide and lactic acid, which in turn provide an acidic environment responsible for a pH typically between 4 and 4.5, thereby avoiding the overgrowth of other pathogenic bacteria [7].

In bacterial vaginosis (BV), there is an alteration of the normal vaginal flora, characterized by an unrestricted overgrowth of anaerobic species, including *Gardnerella vaginalis*, *Bacteroides* species, *Mobiluncus* species, and genital mycoplasma with a concomitant reduction in the number of lactobacilli [8]. The ultimate cause of the vaginal microbiota shift is not completely understood.

BV is the most common cause of vaginitis and accounts for 22–50% of cases depending on the population studied [3, 5]. It is not considered a sexually transmitted disease, however is associated with having more than one sexual partner, a new sex partner in the last 30 days, and having a female sexual partner [9]. Treatment of male sex partners has not been beneficial in preventing the recurrence of BV [10]. Another known risk factor for BV is douching [9], likely due to the alteration of the microsystem with the use of such products.

Not only can BV be bothersome or stressful for women, but it may also increase the risk of complications after gynecologic surgery and complications in pregnancy [11, 12] and increase the risk of HIV acquisition after exposure [13] as well as HIV transmission to male sex partners [14]. Due to the conflicting results of studies regarding treating BV in asymptomatic pregnant women, the latest CDC recommendation states that evidence is insufficient to recommend routine screening for BV in asymptomatic pregnant women at risk for preterm delivery [15].

The typical presentation of BV is characterized by increased vaginal discharge and perceived malodor [3]. Among the prevailing conditions in the patient who has BV

are an elevated pH level (range, 5–5.5) and the presence of various primary amines and polyamines detected by a "fishy odor" after KOH has been added to a sample of discharge [7]. This explains why some women note this odor more when the vagina is more alkaline like after menses or having sex. However, an alkaline pH and even a positive whiff test [can also be present in trichomoniasis].

The Amsel criteria was proposed in 1983 and BV is diagnosed when three of four of the following findings are present 1. thin, homogeneous vaginal discharge; 2. vaginal pH higher than 4.5; 3. release of a fishy odor from the vaginal discharge on alkalinization with 10% potassium hydroxide ("whiff test"); 4. vaginal epithelial cells heavily coated with bacilli (clue cells) [16].

Other microscopy findings highly associated with bacterial vaginosis are scant or lack of lactobacilli (sensitivity 90%, LR 3.1) and the presence of bacilli with corkscrew motility (100% specific, LR 44) [3].

Vulvovaginal Candidiasis

Vulvovaginal candidiasis represents the second most common cause of vaginitis with prevalence between 17% and 39% of cases and affects 70 and 75% of women at least once during their lifetime [17]. Characteristic signs and symptoms include a cheesy vaginal discharge, vulvar pruritus, and vulvar erythema [3]. The term vulvovaginal candidiasis (VVC) was introduced to emphasize the "vulvar" and often dominant component of symptomatic infection [18].

With the availability of over-the-counter antifungals since 1992, most symptomatic women seek these products before or in addition to an evaluation by a medical provider [19]. Women who complain of having "another" yeast infection are indeed likely to have candidiasis as evidenced by a positive likelihood ratio of 3.3 [3].

The majority of cases of VVC are caused by *C. albicans*, and among the non-albicans *Candida* spp., *Candida glabrata*

is the most common [17]. *Candida albicans* has been found in vaginal flora specimens of asymptomatic women and even in stable association with the genital epithelium. This demonstrates that the pathogenicity of such organisms can be highly dependent on host physiology [7].

A precipitating factor is not found in the majority of women with sporadic VVC episodes [18]. Attention to some associated risk factors can become important in cases of complicated or recurrent VVC, as it appears below [17]:

- Uncontrolled diabetes mellitus.
- Antibiotic use, especially in *Candida*-colonized individuals.
- Pregnancy.
- Use of oral contraceptives and contraceptive devices has shown conflicting data.
- Immunosuppression and use of immunosuppressive drugs like glucocorticoids.
- Receptive orogenital sexual intercourse.
- Frequency/periodicity of sexual intercourse.

However women who are not sexually active may develop VVC as well, and contrary to common belief, there is no increased risk among wearers of tight clothing or non-cotton underwear.

The classification of VVC determines the treatment choice: short-course antifungal in uncomplicated cases and intensive regimens in complicated cases [17, 18]. (Table 26.1).

Vaginal Trichomoniasis

Trichomoniasis is caused by the motile protozoan *Trichomonas vaginalis* and is the most prevalent nonviral sexually transmitted infection in the United States [4]. Incubation of *T. vaginalis* requires 3 days to 4 weeks, and the vagina, urethra, endocervix, and bladder can be infected [6]. Up to half of women infected with *Trichomonas* are asymptomatic and if left untreated can be carriers for at least 3 months even in the absence or reexposure [20]. Signs and symptoms are not

Table 26.1 Classification for vulvovaginal candidiasis

Uncomplicated (topical agents)	Complicated (oral agents)
• Sporadic or infrequent (≤ 3 episodes/year) • Mild to moderate severity • Likely to be *C. albicans* • Healthy, nonpregnant host	• Recurrent (≥ 4 episodes/year) • Moderate to severe disease • Non-albicans candidiasis • Adverse host factors (e.g., pregnancy, poorly controlled diabetes, immunosuppression)

specific, but the classic presentation can include green–yellow and frothy vaginal discharge, vaginal irritation, vaginal spotting, dyspareunia, and dysuria. Additionally signs of vulvar inflammation can be present, and if the cervix is affected, subepithelial hemorrhages can be seen as the typical "strawberry cervix" [1, 6, 21].

T. vaginalis infection is associated with two- to threefold increased risk for HIV acquisition and preterm delivery and among HIV-positive women is associated with increased risk for pelvic inflammatory disease [4, 22]. The CDC recommends routine screening in all asymptomatic women with HIV infection, and screening might be considered for persons receiving care in high-prevalence settings, such as STI (sexually transmitted infection) clinics or correctional facilities, and for asymptomatic individual at high risk for STIs (e.g., multiple sex partners, exchanging sex for payment, illicit drug use, or a history of STI).

Treatment of sexual partners and abstinence from sex should be recommended until treatment is achieved, and testing for other STIs should be performed. Appropriate follow-up includes retesting within 3 months after treatment due to the high rates of reinfection; if NAAT (nucleic acid amplification test) is used, patients can be tested 2 weeks after finishing treatment. Trichomoniasis is not a national notifiable infection in the United States.

Other Infectious Causes of Vaginitis

Some conditions that can present as vaginal complaints are chlamydia, gonorrhea, herpes, and papillomatosis. All of these will be suggested after doing a pelvic examination by the presence of papillomas or vesicles in the introitus, or in the case of chlamydia and gonorrhea, the discharge will be coming from the os of the cervix, and the patient may or may not have cervical tenderness.

Noninfectious Causes Of Vaginitis

Atrophic vaginitis is a highly prevalent and underdiagnosed condition that impacts quality of life of many women. An international survey done by Nappi et al. found that about 40% of women have menopause-related vaginal discomfort yet less than one-third had discussed these symptoms with their primary care doctor [23]. Vaginal symptoms of atrophic vaginitis include vaginal pruritus, abnormal discharge, vaginal dryness, irritation, and dyspareunia.

As the estrogen stimulation decreases, the vulvovaginal epithelium becomes atrophic and there is loss of mucosal elasticity. The mucosa of the vagina, introitus, and labia minora appears smooth, pale, and shiny. Inflammation with patchy erythema, petechiae, and increased friability may be present. Vulvar signs of irritation caused by urinary incontinence may also be identified on pelvic examination. The vaginal pH becomes more alkaline due to the drop in glycogen levels and decreased production of lactic acid by lactobacilli. Cytologic examination of smears from the upper one-third of the vagina shows an increased proportion of parabasal cells and a decreased percentage of superficial cells [24, 25].

Other noninfectious causes of vaginal complaints can be initiated by allergic contact dermatitis or irritant contact dermatitis from hygiene products, contraceptive devices, or even retained foreign material such as tampons or condoms.

Key History and Physical Exam

The typical signs and symptoms of each cause of vaginitis have been mentioned in the previous pages, but in summary the symptoms to elicit from patients include the characteristics of the discharge (color, consistency, quantity, abnormal odor) and presence of vaginal pruritus or irritation, along with other symptoms such as dysuria and dyspareunia and if the patient has used any over-the-counter medication prior to presentation. In Table 26.2 there is a list of some of the signs and symptoms that have been shown to have a good predictive value for the three most common causes of infectious vaginitis. It is also good practice to obtain a sexual history to determine the patient's risk of having a current sexually transmitted disease by asking the five Ps: partners, practice, prevention of pregnancy, protection from STIs, and past history of STIs.

When performing a pelvic examination, inspect the vulva for signs of inflammation such as erythema, edema, and excoriation as well as for the presence of vesicular lesions or papillomas.

After insertion of the speculum, if discharge is present, the source should be determined (e.g., cervical os suggests a cervicitis as opposed to a vaginitis). The vaginal walls and the cervix should be examined for signs of inflammation or friability, noting the characteristics of the discharge. Finally the presence of cervical motion tenderness should be evaluated.

For pH and microscopy testing, discharge should be sampled from the sidewall of the vagina. If purulent cervical discharge is noted, make sure to obtain a sample to test for chlamydia and gonorrhea.

Table 26.2 Likelihood ratios of different vaginal complaints

Diagnosis	Vaginal complaint	Likelihood ratio LR (95% CI)
Candidiasis	Itching (chief complaint)	3.3 (2.4–4.8)
	Curdy discharge	6.1 (2.5–14)
	Vulvovaginal inflammatory signs	2.1–8.4 (1.3–16)
	Self-diagnosis	3.3 (1.2–9.1)
	Curdy discharge and itching	150 (20–1000)
Bacterial vaginosis	Odor noted by clinician	3.2 (2.1–4.7)
Trichomoniasis	Erythema or edema	6.4 (1.6–26)

Adapted from Anderson MR, Klink K, Cohrssen A. Evaluation of vaginal complaints. JAMA 2004;291(11):1368–1379

Diagnostic Evaluation

A good history and physical examination will provide clues into the cause of the vaginal complaints, but it is imperative to mention that no symptom has enough predictive power to make a diagnosis.

1. Assess the vaginal pH; a normal pH (< 4.5) will point toward VVC and a pH > 4.5 can be due to BV or TV (*Trichomonas vaginalis*).
2. Wet mount microscopic examination:
   - Trichomonads (sensitivity 51%–65%, but 100% specific). Evaluate slides immediately because sensitivity for trichomoniasis declines as evaluation is delayed, decreasing by up to 20% within 1 h after collection.
   - Clue cells (vaginal squamous epithelial cells with copious adherent coccobacilli).
   - Yeast (hyphae or spores).

3. Add 10% potassium hydroxide (KOH) to a drop of vaginal discharge and "whiff" the sample. If a fishy odor is present, that constitutes a positive "whiff test."

Next, take the slide to the microscope; the use of KOH will make yeast more visible (sensitivity 38–83% and specificity 77–94%).

BV can be diagnosed if three of four Amsel criteria are present: vaginal pH > 4.5, thin watery discharge, positive whiff test, and wet mount with > 20% clue cells. In a prospective observational study, a vaginal pH of more than 4.5 was found to be the most sensitive (89%), and a positive whiff test was the most specific (93%) method of detecting BV [26]. Culture of *G. vaginalis* is not recommended as a diagnostic tool because of its low specificity [1].

If preliminary tests are inconclusive, further testing should be performed. If pH is normal, then obtain a culture for vulvovaginal candidiasis. Unfortunately, up to 50% of patients with culture-positive symptomatic VVC will have negative microscopy [17]. If the pH was > 4.5 but the Amsel criteria was not fulfilled or patient has risks for STIs, then perform further testing for trichomoniasis. Culture was considered the gold standard method for diagnosing *T. vaginalis* infection before molecular detection methods became available. Culture has a sensitivity of 75–96% and a specificity of up to 100%, but nucleic acid amplification test (NAAT) is highly sensitive, often detecting three to five times more *T. vaginalis* infections than wet mount microscopy (Fig. 26.1).

Treatment

See the 2015 CDC guidelines as described below in Table 26.3 [4]. Recurrent vulvovaginal candidiasis is treated with either oral or topical azole and continued until the patient is asymptomatic and culture negative. Ongoing suppressive regimens include once weekly dosing of either 500 mg clotrimazole suppositories or 150 mg fluconazole orally [17].

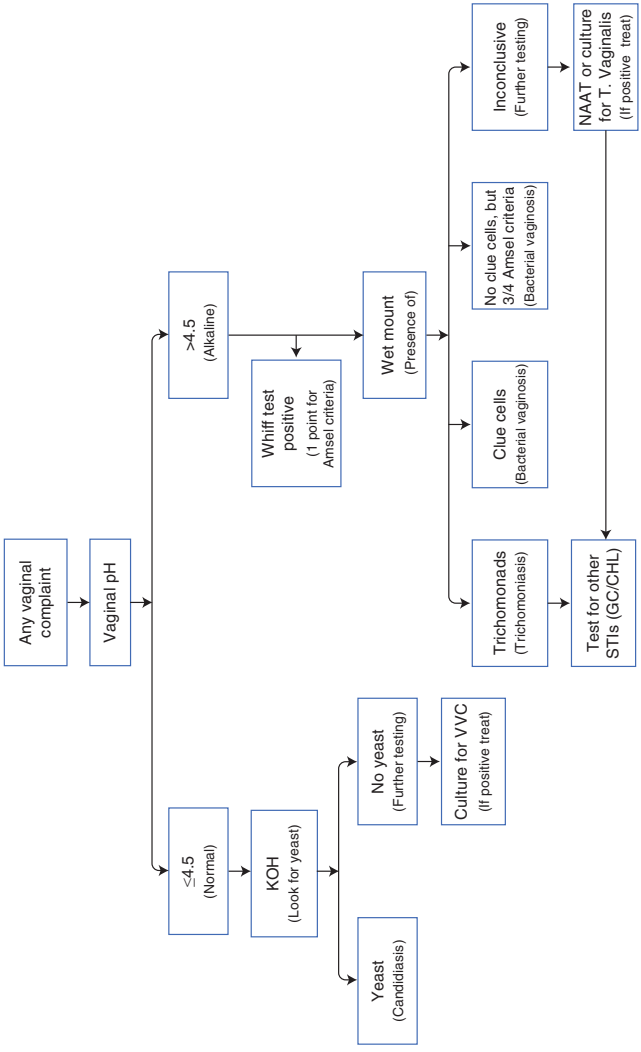

FIG. 26.1 Vaginitis algorithm

TABLE 26.3 Sexually transmitted disease treatment guidelines, 2015

Pathogen	Recommended regimens	Alternative regimens	Other considerations
Bacterial vaginosis	• *Metronidazole* 500 mg orally twice a day for 7 days OR • *Metronidazole* gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 daysOR • *Clindamycin* cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days	• *Tinidazole* 2 g orally once daily for 2 days OR • *Tinidazole* 1 g orally once daily for 5 days OR • *Clindamycin* 300 mg orally twice daily for 7 days OR • *Clindamycin* ovules 100 mg intravaginally at bedtime for 3 days*	• Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and vaginal contraceptive diaphragms). The use of such products within 72 h following treatment with clindamycin ovules is not recommended • Tinidazole should be avoided during pregnancy
Trichomoniasis	• *Metronidazole* 2 g orally in a single dose OR • *Tinidazole* 2 g orally in a single dose	• *Metronidazole* 500 mg orally twice a day for 7 days	• Treat sexual partner • Consider delaying breastfeeding for 12–24 h following maternal treatment of a single 2 g dose of metronidazole • Tinidazole should be avoided during pregnancy

(continued)

Table 26.3 (continued)

Pathogen	Recommended regimens	Alternative regimens	Other considerations
Candidiasis	Over-the-counter intravaginal agents: (any one of the following) *Clotrimazole* 2% cream 5 g intravaginally daily for 3 days *Miconazole* 4% cream 5 g intravaginally daily for 3 days *Miconazole* 200 mg vaginal suppository, one suppository for 3 days *Miconazole* 1200 mg vaginal suppository, one suppository for 1 day *Tioconazole* 6.5% ointment 5 g intravaginally in a single application *Prescription intravaginal agents:* Oral agent: *Fluconazole* 150 mg orally in a single dose Topicals: *Terconazole* 0.8% cream 5 g intravaginally daily for 3 days *Terconazole* 80 mg vaginal suppository, one suppository daily for 3 days		• The creams and suppositories in these regimens are oil based and might weaken latex condoms and diaphragms

Pathogen	Recommended regimens	Alternative regimens	Other considerations
Gonorrhea	*Ceftriaxone* 250 mg IM	*Cefixime* 400 mg orally in a single dose	Without cultures, empirically treat for chlamydia as well
Chlamydia	*Azithromycin* 1 gm PO single dose	*Doxycycline* 100 mg twice a day for 7 days	Without cultures, empirically treat for gonorrhea as well
Genital herpes (first episode)	*Acyclovir 400 mg PO TID* for 7–10 days *Valacyclovir 1 g PO BID* for 7–10 days		Treatment can be extended if healing is incomplete after 10 days of therapy.
Genital herpes (suppressive therapy)	*Acyclovir 400 mg PO BID* *Valacyclovir 1 g PO once a day*		Suppressive therapy is encouraged in discordant couples to decrease the rate of transmission, along with condom use and abstinence during recurrence.
Genital herpes (episodic therapy for recurrent herpes)	*Acyclovir 400 mg PO TID* for 5 days *Valacyclovir 1 g PO once a day* for 5 days		

*Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and vaginal contraceptive diaphragms). Use of such products within 72 hours following treatment with clindamycin ovules is not recommended.

Treatment for atrophic vaginitis includes topical estrogen for women without contraindications or vaginal lubricant in women who prefer not to use estrogens.

Clinical Pearls

- All women with vaginal complaints should undergo at a minimum pelvic examination and office-based microscopy before starting treatment, given that no symptom has enough predictive power to make a diagnosis.
- The three most common causes of infectious vaginitis are bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis.
- The presence of vaginal pruritus, curdy discharge, and a normal pH is highly suggestive of vulvovaginal candidiasis.
- Classifying vulvovaginal candidiasis as noncomplicated or complicated will aid in the choice of treatment.
- Bacterial vaginosis and *T. vaginalis* increase the risk of HIV acquisition and transmission and are associated with adverse pregnancy outcomes.

Don't Miss This!

- If trichomoniasis is diagnosed, be certain to test for other STIs and treat the sexual partner(s).
- Patients with cervical discharge with or without systemic symptoms need to be evaluated for GC/CHL.
- Patients with cervical discharge and cervical motion tenderness should be treated for GC/CHL empirically.

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Chapter 27
Contraception

Athina Vassilakis

Introduction

About 42 million sexually active women in the USA are at risk for an unwanted pregnancy without adequate contraception use [1, 2]. Certain medical conditions also render pregnancy high risk, such that birth control can 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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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_27

Decision-Making

Contraception visits should start with establishing 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. 27.1).

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 non-contraceptive health benefits, interval for thinking about contraception, bleeding patterns, side effects, comfort, practicality of use, and hormonal vs. non-hormonal methods [4]. For adolescents, issues of cognitive development and reliability, high-risk behavior, and confidentiality (including use of parent insurance) need to be considered [5].

Key History and Physical Exam

To establish reasonable certainty that a woman 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, or at least nearly fully breastfeeding [6, 7]. Alternatively, a pregnancy test can be obtained.

Additional history and examination should focus on safety and self-determination, patient preferences, and pos-

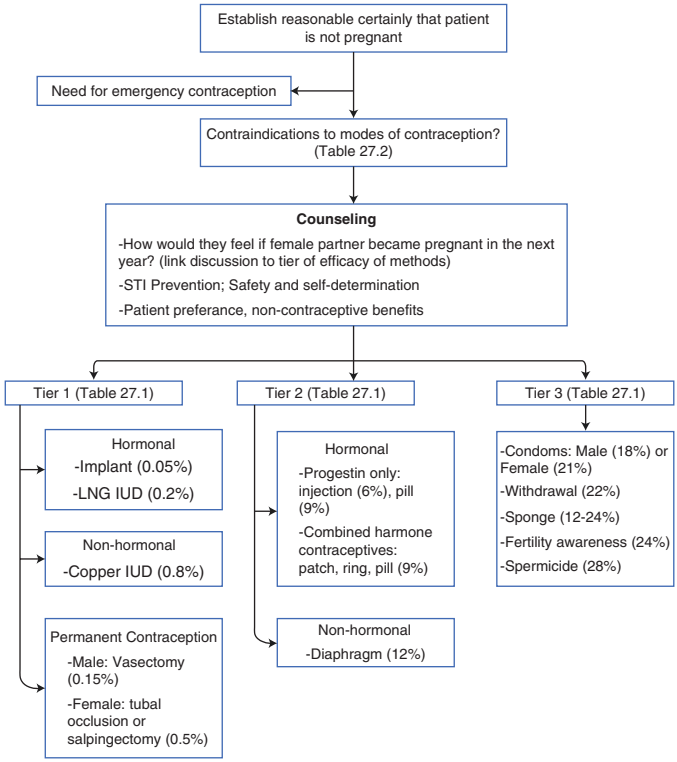

FIG. 27.1 Contraception choice. Percentages are of women becoming pregnant within one year of typical use, which can be significantly higher than failure rates with perfect use of these methods

sible 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, as well as 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 27.1. Table 27.2 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. Lesnewsky et al. provide detailed information on preventing contraception gaps when switching methods of contraception [9].

Progestin implant is the most efficacious, reversible method of contraception available at this time [10]. A small rod containing etonogestrel is placed subcutaneously in the inner aspect of the woman's 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 [5, 7, 11].

Permanent contraception options for women 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% [12]. Intraperitoneal adhesions can complicate these procedures. Hysteroscopic tubal occlusion (Essure) involves placing a nickel–titanium coil that induces intratubal fibrosis under local anesthesia. It takes time to occlude the tubes and requires a confirmatory salpingogram 3 months after placement [13].

Intrauterine device (IUD) use is now recommended as a first-line method of contraception, especially for teenagers, nulliparous women, and women infected with HIV [14, 15]. 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

TABLE 27.1 Contraceptive modes available by efficacy tiers (color code)

Method	Failure rate[c]	Time to effectiveness	Possible side effects	General tips/routine follow-up evaluation
Implant	0.05%	7 days[a]	– 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 method – Approved for 3 years, effective up to 5 years in small studies
Vasectomy	0.15%	4 months	– Chronic testicular discomfort in 15% overall, 0.9% severe	– Vasovasostomy, when available, can at times return fertility—subsequent pregnancy rates range33–64%.
Abdominal/ laparoscopic	0.5%	Immediate	– Surgery complication, blood transfusion, infection, ectopic pregnancy, anesthesia complications	– Only postoperative follow–up
Hysteroscopy	0.5%	3 months	– Nickel sensitivity, chronic pain from malposition or expulsion: remove or reposition device – Bowel injury or obstruction	– Requires confirmatory salpingogram in 3 months then no follow–up
Copper IUD (Cu)	0.8%	Immediate	– 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 – LNG approved for 3 or 5 years(different devices) – Cu approved for 10 years, can be efficacious for 12 – Can treat pelvic inflammatory disease without removal of device
LNG IUD	0.2%	7 days[b]		
Injectable progesterone (DMPA)	6%	7 days[b]	– 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	– 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	5– 9%	2 days[a]	– Hirsutism, acne, bleeding: if eligible, consider CHC	Excellent for lactating women
Combined hormonal contraceptive pill, patch, ring	5– 9%	7 days[a]	– 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	12%	Immediate	– Vaginal irritation from spermicide	– Use spermicide with each new encounter while in place and keep for 6 h after last intercourse
Condom	14–21%	Immediate	– Latex allergies	– Prevents sexual transmitted diseases – Female condoms usually not latex
Withdrawal	22%	Immediate		– Requires partner compliance and body awareness
Sponge	12–24%	Immediate	– Vaginal irritation from spermicide	– Effective for 24 h. Keep 6 h post intercourse – Much less effective in parous women
Fertility awareness	25%	Immediate after period		– Various methods available
Spermicide	28%	Immediate	–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 27.2 Category 3 (risks usually outweigh the advantages) or 4 conditions (unacceptable health risk) 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*, liver disease,[a] history of stroke*, SLE with antiphospholipid antibody, anticonvulsant use, rifampin/rifabutin use, history of breast cancer, bariatric surgery causing malabsorption (pill only), unexplained vaginal bleeding (implant only). *Pill or implant can be initiated for short-term acute benefits, but should not be continued for prolonged periods of time.

(continued)

Table 27.2 (continued)

Contraceptive method	Contraindications or precautions (method contraindicated or risks likely outweigh the benefits)
IUD	Pelvic, uterine, or cervical distortion, cancer, or acute infection,[a] 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,[a] 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,[a] diabetes with complications,[b] 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.
Combined hormone contraception (pill, ring, patch)	Hypertension (even controlled), high risk for or current acute thrombosis,[a] ischemic heart disease, liver disease,[a] high risk for coronary artery disease, peripartum cardiomyopathy, smoking and age > 34, history of stroke, diabetes with complications,[b] 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

[a]See original for specific conditions included in this category

[b]Vasculopathy, nephropathy, retinopathy, neuropathy

IUD (LNG-IUD) is available in devices for 3 and 5 years of use. It can take up to 7 days to become effective [5, 7, 15].

Progestin-only pills (POPs) are a good option for postpartum and lactating women and work as well as estrogen-containing products without safety issues. They are taken daily and become effective within 2 days of use [7].

Combined hormonal contraceptives (CHC) are often used for their non-contraceptive 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 [16, 17]. 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 [5, 7, 18]. 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 [7].

Notes on hormonal contraceptives: Data for up to seven years of oral contraceptive use shows no difference in fertility and no concerns for pregnancy outcomes [19]. 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. High estrogen dose CHC increase breast cancer risk slightly. Studies assessing risk of low estrogen dose CHC in women with BRCA mutations show no significant increase in breast cancer incidence from their baseline, but a decreased risk of ovarian cancer [20].

Condoms are the only option to reduce sexually transmitted infections in sexually active people and should be encouraged in addition to all other methods for this purpose.

Emergency contraception (EC) can prevent unwanted pregnancy after sexual intercourse. It should not be used for routine contraception because it is not as effective as regular contraceptive methods. 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. Women 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 [7, 21]. Combination oral contraceptives can also be used, but they are less efficacious. Specific dosing options can be found at http://ec.princeton.edu/questions/dose.html. 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 women with BMI over 30 (ulipristol 2.6% failure, levonorgestrel 5.6% failure) [22]. 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 efficacy of this practice has not yet been demonstrated [21].

Clinical Pearls

- IUDs and implants are recommended as first-line, reversible modes of contraception for most women.

- Start by asking women how they would feel if they became pregnant in the next year.
- Use tiers of effectiveness to present contraceptive methods.

Don't Miss This!

- Opportunities to promote discussions about contraception in the clinic—flyers, pamphlets.
- Teenager confidentiality—know state laws, decide whether to use parent insurance.
- Contraception gaps when initiating or switching methods of contraception.
- Offer contraception to women with serious medical problems to prevent complications.

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Part IX
Genitourinary

Chapter 28
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.

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_28

Decision-Making/Differential Diagnosis

The evaluation of dysuria is quite different 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 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 gonorrhea*
      - *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 is 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 [10].

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, usually infectious due to *Chlamydia* and *Neisseria* 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 [11].
- 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 [12].

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. 28.1).
- Atrophic vaginitis: a common postmenopausal disorder characterized by dryness, inflammation, and thinning of vaginal mucosa.
- Endometriosis: urinary tract endometriosis may present with dysuria as well as abdominal pain and menorrhagia.
- 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

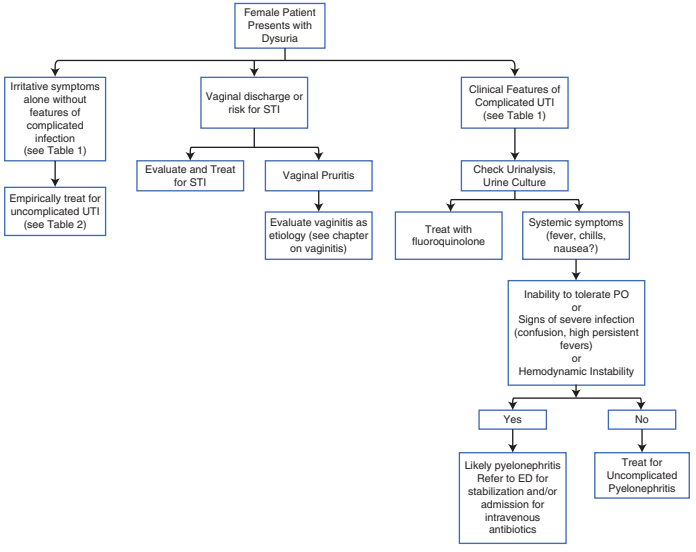

FIG. 28.1 Approach to the female patient with dysuria

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 [13] (Table 28.1).

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 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,

Table 28.1 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

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. 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

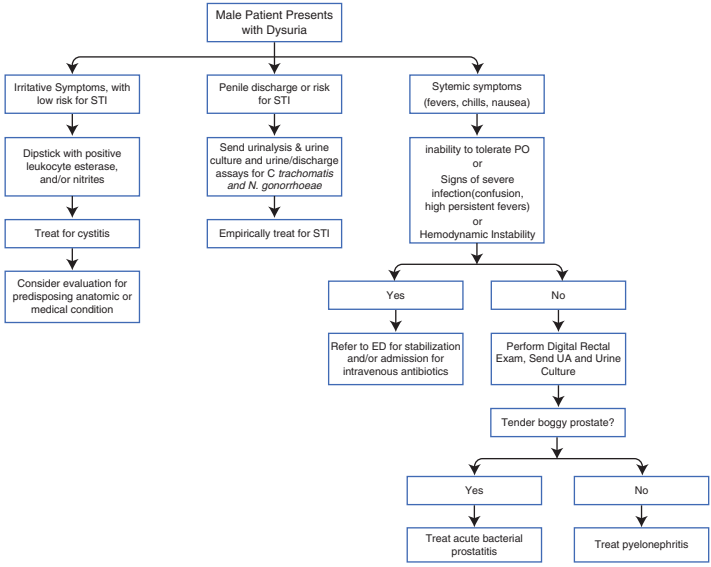

FIG. 28.2 Approach to the male patient with dysuria

indicated if patient has limb complaints to identify joint effusions or tenosynovitis (Fig. 28.2).

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 performed. 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 28.2 [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 28.2) 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 [15]:

- 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 28.2 Treatment of uncomplicated UTI in women, adapted from 2011 IDSA guidelines [15]

	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

Second-line	Fluoroquinolones • Ciprofloxacin, 500 mg twice daily, 3 days • Levofloxacin, 250 mg once daily, 3 days • Ofloxacin, 200 mg, twice daily, 3 days	Common SEs: gastrointestinal upset and neurologic symptoms like headache or dizziness Severe SE are rare but include rashes/allergic reactions, tendonitis, tendon rupture, QT prolongation, and transaminitis	Should only be used if first-line agent is unavailable or not suitable due to allergy; increasing fluoroquinolone resistance is noted
	Beta-lactams • 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	Common SEs: diarrhea, IgE-mediated allergies ranging in severity from pruritus flushing (common) to anaphylaxis (rare) Severe SEs include encephalopathy and Stevens-Johnson syndrome	All are less effective than agents listed above and are associated with significant adverse effects

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 single intramuscular dose of ceftriaxone 250 mg with a single oral dose of azithromycin 1g is the preferred regimen for treating these two common STIs [7]. A 7-day course of doxycycline 100 mg is equally as effective as azithromycin 1g and is the preferred addition to ceftriaxone for sexually transmitted epididymo-orchitis [7]. Epididymitis due to enteric organisms should be treated with a fluoroquinolone such as levofloxacin 500 mg orally once daily for 10 days [7]. 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 250 mg plus once-daily levofloxacin 500 mg × 10 days [7]. For bacterial vaginosis and trichomoniasis, metronidazole 500 mg twice daily for 7 days is the preferred agent (the latter may be treated with a single 2 g oral dose) [7]. 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 text.

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, 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.

Don't Miss This!

- Pyelonephritis
- Sexually transmitted infections and HIV
- Acute bacterial prostatitis
- Bladder or renal cancer

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Chapter 29
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 29.1 and 29.2). 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]. KDIGO criteria combine RIFLE and AKIN criteria [3] (Table 29.2). Although serum

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_29

Table 29.1 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]

creatinine is a commonly used marker for kidney function, it has several limitations. Gender and muscle mass can influence the serum creatinine value; lower levels are observed in females, malnourished patients, and in 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]. 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

TABLE 29.2 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, decrease in eGFR to < 35 mL/min per 1.73 m^2	< 0.3 mL/kg/h × ≥ 24 h or anuria × ≥ 12 h

eGFR estimated glomerular filtration rate, *RRT* renal replacement therapy

serum creatinine is not available. Sonographic findings of small echogenic kidneys and laboratory evidence of anemia and secondary hyperparathyroidism are suggestive of CKD.

Differential Diagnosis

AKI is classified into prerenal, intrinsic, and postrenal depending on the etiology (Algorithm 1, Fig. 29.1) [8, 9]. Prerenal AKI results from compromised renal perfusion due to decreased volume (from gastrointestinal or renal losses), effective volume depletion (seen in patients with congestive

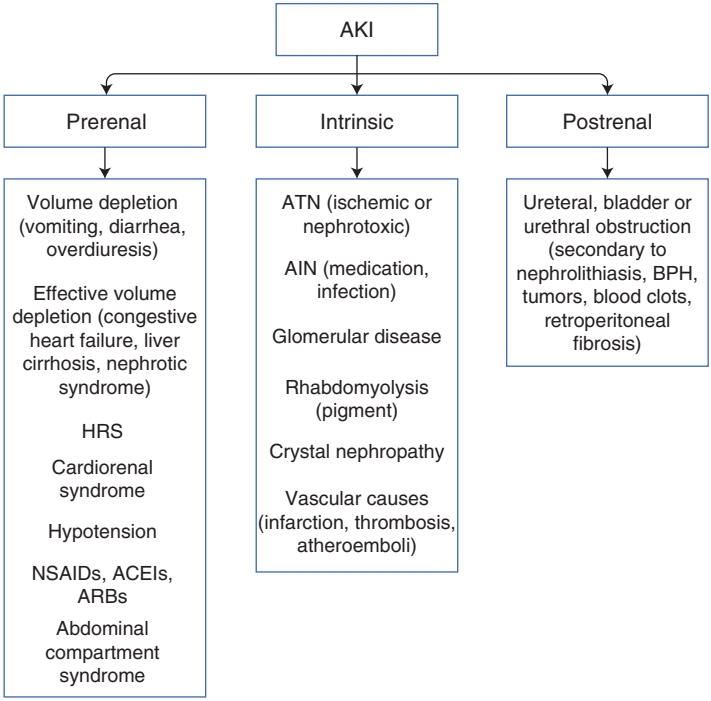

Fig. 29.1 Classification of AKI into prerenal, intrinsic, and postrenal

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]. 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]. Glomerulonephritis is characterized by proteinuria, hematuria, and presence of dysmorphic red blood cells (RBCs) and RBC casts in the urinary sediment. Vascular events such as acute renal infarction, renal vein thrombosis and atheroemboli are other causes of intrinsic AKI.

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. 29.1)

Key History and Physical Exam

A detailed history focused on certain symptoms is essential (Fig. 29.2) [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 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. 29.3) 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

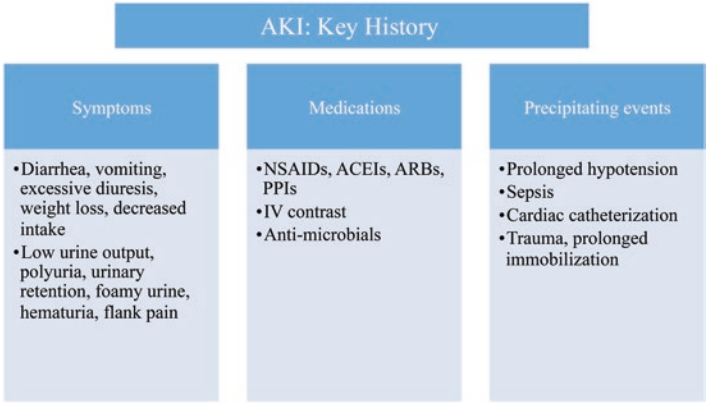

FIG. 29.2 Key elements in the history taking of a patient with AKI

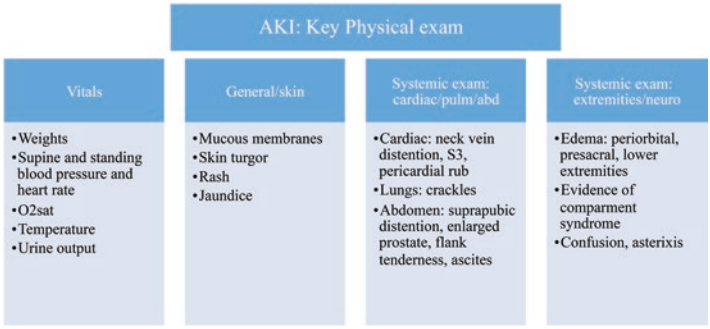

FIG. 29.3 Key elements in the physical examination of a patient with AKI

decreased skin turgor). A thorough exam should evaluate for flank tenderness and for the presence of 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. In those with history of trauma or recent surgery, the clinician should assess for presence of compartment syndrome on physical exam.

Decision-Making/Treatment

The initial work-up of AKI involves the evaluation of a urinalysis (UA) to assess the urine specific gravity, pH, and for the presence of proteinuria, hematuria, and pyuria (Algorithm 2, Fig. 29.4) [8]. 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

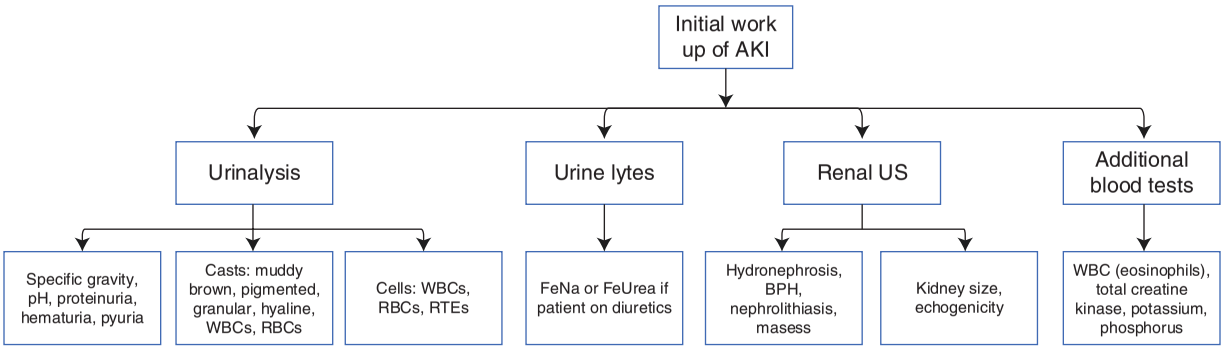

FIG. 29.4 Initial laboratory and radiologic testing in a patient with AKI

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].

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. Lastly, kidney biopsy may be necessary if the cause of AKI remains unclear (Fig. 29.4).

The treatment of AKI is directed toward correcting the underlying etiology and providing supportive measures. Other important steps include as follows:

- Prompt relief of obstruction and monitoring for post obstructive diuresis.
- Avoiding further nephrotoxins is essential.
- Medications should be dosed for the patient's renal function (based on either creatinine clearance or estimated GFR).
- 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 [15].
- 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 per 1.73 m^2) and recommended for those with stage 4 CKD (GFR < 30 mL/min per 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.

Don't Miss This!

- Watch for indications for dialysis: refractory hyperkalemia/severe acidosis, uremic encephalopathy/pericarditis, refractory volume overload.
- Review the medications the patient has been taking, and don't 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 30
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 30.1) [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

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_30

Table 30.1 NIH classification of prostatitis (1999)

I.	Acute bacterial prostatitis
II.	Chronic bacterial prostatitis
III.	Chronic prostatitis/chronic pelvic pain syndrome
	A. Inflammatory
	B. Noninflammatory
IV.	Asymptomatic inflammatory prostatitis

discussed further as it has not been sufficiently studied to determine natural history or need for treatment.

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. 30.1).

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 suspicion for bacteremia (persistent fevers or chills) or if they cannot tolerate oral medications. Failed outpatient management is also an indication for admission [3].

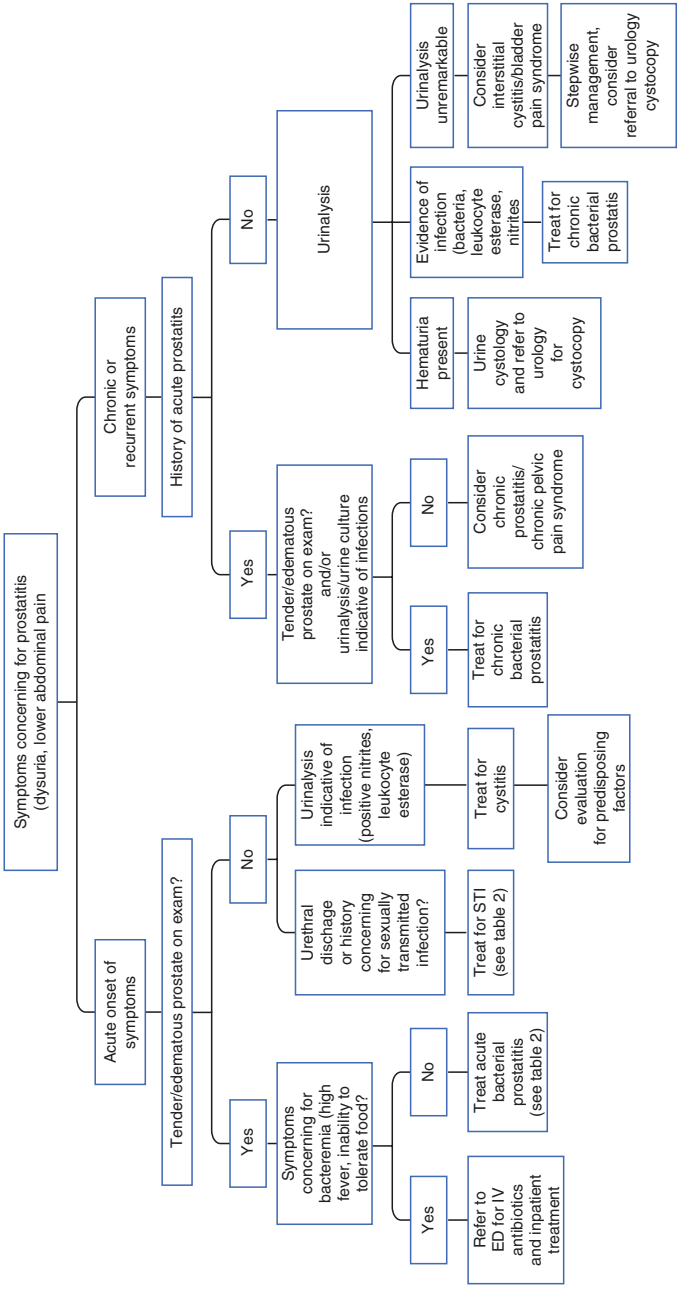

FIG. 30.1 Approach to patient with symptoms concerning for prostatitis

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 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 gonorrhea* and *Chlamydia trachomatis* PCR testing if indicated. Urine cytology may be considered if hematuria and risk factors for bladder cancer (smoking, age >40) are present. Serum levels of prostatic 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 30.2 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.

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

Table 30.2 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

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 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 for 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. 30.2)

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 thera-

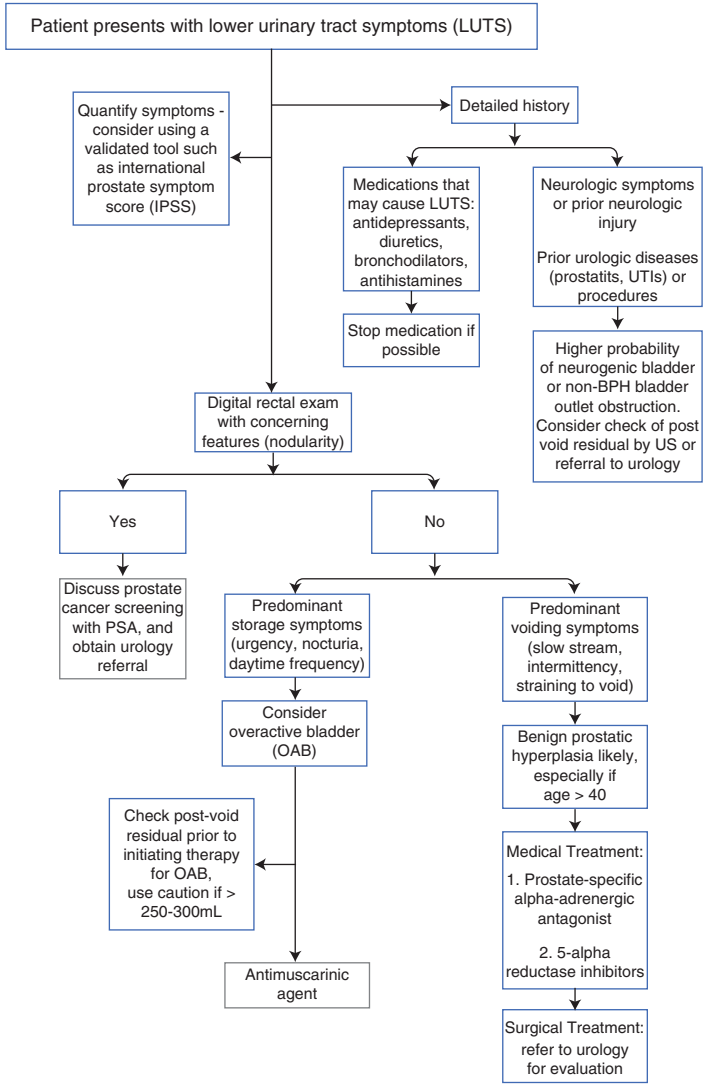

FIG. 30.2 Approach to patient with lower urinary tract symptoms

peutic 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 180,000 new cases in 2016 [19]. The majority of cases are diagnosed in men older than 60. 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 screen-

ing 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 as well as high morbidity from prostate cancer treatment including operative mortality and postoperative incontinence, sexual dysfunction, and bowel problems [22]. Due to these complexities, the US Preventive Services Task Force (USPSTF), the panel which makes evidenced based recommendations for various screening tests, has given PSA screening a grade D, recommending against the service [23]. The American Urological Association (AUA) 2013 consensus statement recommends shared decision-making for men aged 55–69 and to avoid routine screening with PSA outside of this age group [24].

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 [25]. 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 [26]. 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 [27].

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 urinary 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.

Don't Miss This!

- Acute bacterial prostatitis can present with lower abdominal and pelvic pain.
- Prostatic abscess may be the problem in men who don't respond to initial course of antibiotics.
- Sexually transmitted infections like *Neisseria gonorrhea*, *Chlaymdia 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 31
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 considered chronic. In the primary care setting, in about

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© Springer International Publishing AG 2018

E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_31

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 begins with inspection to assess the acuity of the pain and if there is evidence of peritoneal inflammation or irritation. The intensity of the pain is less helpful in this situation than the fact that the pain is made worse with any pressure changes in the abdomen, such as with palpation, coughing, or movement [3]. Thus the patient with peritonitis will lie quietly, avoiding movement, and will likely exhibit considerable guarding (tensing of the abdominal wall musculature) upon examination and rebound tenderness. The presence or quality of bowel sounds does not significantly aid in diagnosis [3], although a completely quiet abdomen is consistent with severe peritonitis. Otherwise, specific abdominal signs may be minimal.

Other acute abdominal symptoms may be related to either complete or partial obstruction of a hollow viscus. This pain usually comes in waves, intermittently, and thus is referred to as *colicky* pain. Patients with colic pain will usually be unable to sit still and may be restless [3]. This pain may be related to

a gastrointestinal, biliary, genitourinary, or gynecologic process, although it may be less well localized than peritoneal pain 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), costovertebral angle tenderness, and sensory evaluation 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 non-localized pain allows for an initial differential diagnosis (see Fig. 31.1). Physical examination in patients with abdominal pain has low specificity and low sensitivity, 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

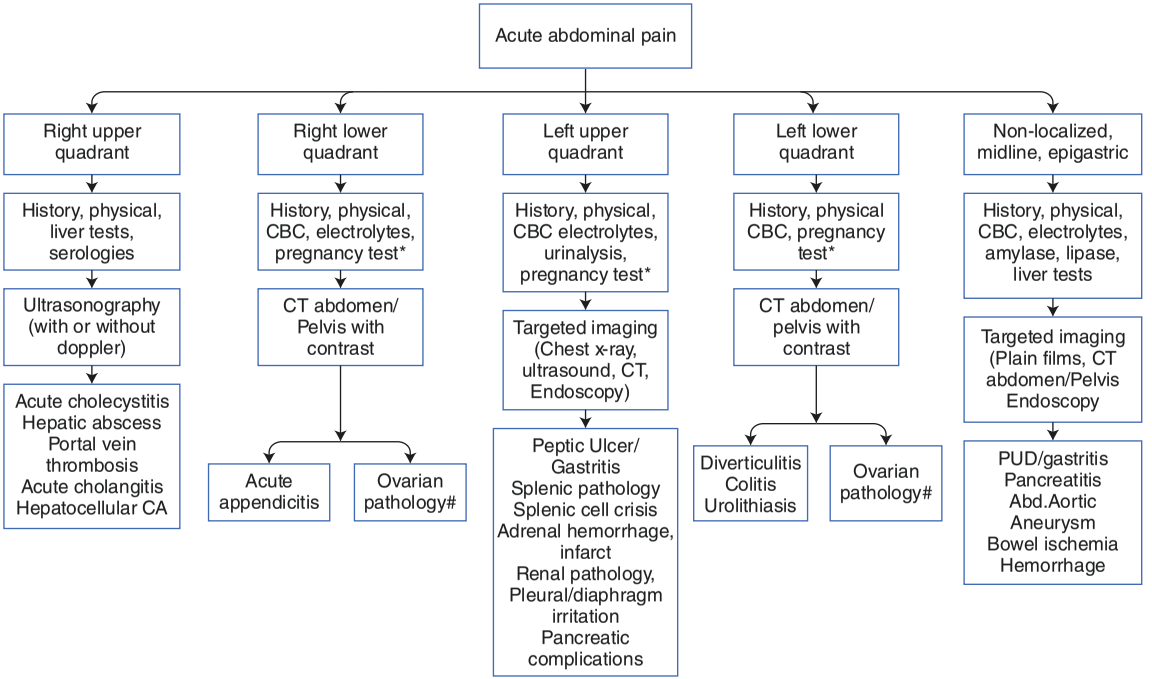

FIG. 31.1 Acute abdominal pain evaluation. (*Asterisks*) Substitute ultrasound or MRI for pregnant patients with acute abdominal pain requiring imaging. (*Ampersand*) Denotes ovarian torsion, ovarian cyst, or ectopic pregnancy. Pelvic inflammatory disease may be diagnosed by pelvic examination and does not require imaging

decreasing radiation exposure, magnetic resonance imaging (MRI) and ultrasound have been utilized more, reserving CT only for nondiagnostic studies in selected cases.

Chronic abdominal pain requires a different approach (see Fig. 31.2). 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, 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].

Decision-Making/Differential Diagnosis

Patients with 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

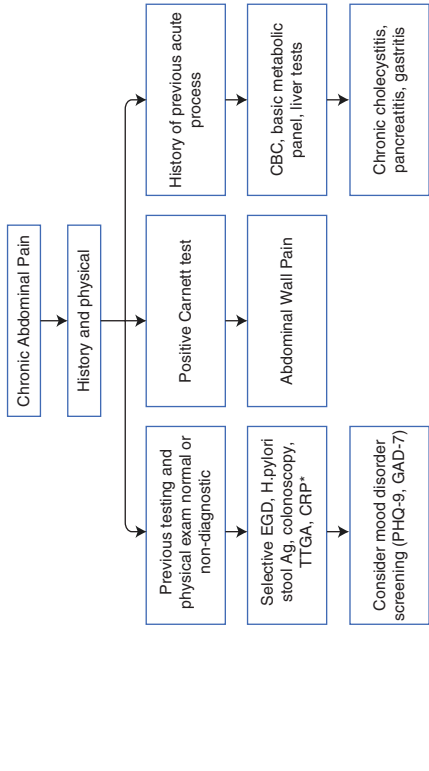

FIG. 31.2 Chronic abdominal pain evaluation. (*Asterisks*) Based on symptoms and/or to rule out alternative disorders

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 can 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 tried 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 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, but diagnosis is made via imaging. Other causes of RLQ pain include mesenteric adenitis, pelvic pathology, Mekel'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 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 non-localized 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. 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 aneurysms (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 for 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 indicated. 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 reutake 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 neurectomy [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.

Don't 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 32
Abnormal Liver Tests

Sreekala Raghavan and Rosemarie L. Conigliaro

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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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_32

Key History and Physical Exam

Normal test result ranges 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]. Since many patients 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 autoimmune or liver diseases, and a history of risk factors for liver disease, including alcohol history, current and prior 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. These risk factors include intravenous drug use, sexual history, tattoos, nonsterile piercings, transfusions, residence in endemic regions, or having parents from highly endemic regions [2].

In most cases, asymtomatic patients will have a normal physical exam. However, signs of a chronic process should be assessed. Examine for fever, scleral icterus or jaundice, 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 alcoholism. 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 what 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 [3]. 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 [4].

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, measures of clotting factors 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 [3].

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. 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 [5], 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 bili-

rubin 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 [4].

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. 32.1 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 scope of this chapter. The levels 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).

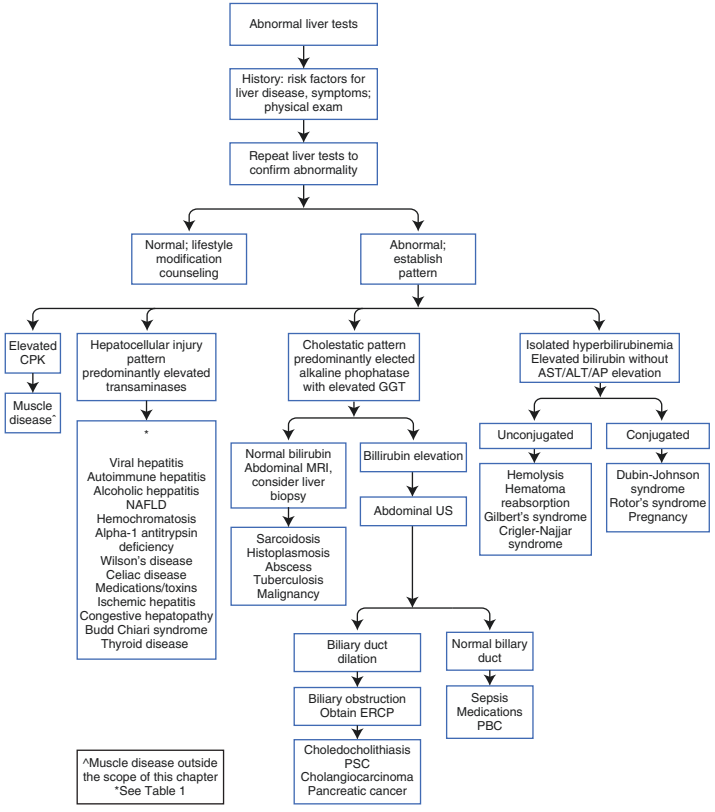

FIG. 32.1 Abnormal liver test evaluation. ^Muscle disease outside the scope of this chapter. *See Table 32.1

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 32.1 [1, 3, 6–8]. Common causes of milder elevations of the AST and

TABLE 32.1 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 (ji bu huan, ephedra), germander, gentian, kava kava, scutellaria, senna, shark cartilage

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 with increasing rates of obesity, with studies showing prevalence from 57.5 to 74% in obese patients. It can be detected as increased echogenicity on abdominal ultrasound although liver biopsy is needed to confirm the diagnosis [6]. 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 aminotrasnferases 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 [9]. A serum thyroid stimulating hormone assesses for thyroid abnormalities, and a transthoracic echocardiogram may be obtained to evaluate for heart failure. See Table 32.2 for further diagnostic workup of hepatocellular injury by etiology.

Table 32.2 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

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 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 retrograde cholangiopancreatography (ERCP) can 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 [3].

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 [3]. 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 [2]. 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 abuse and weight reduction counseling and discontinuation of hepatotoxic substances or medications are important therapeutic measures to undertake in the general medical office. 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 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, patients require hospital admission to identify the cause, to initiate supportive management, or to monitor the need for transplantation. Gilbert's syndrome is often noted in the primary care setting; it is benign. Further specialty care referral is recommended for management of the other genetic disorders of bilirubin metabolism, hereditary disorders such as hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, and also for autoimmune hepatitis.

Clinical Pearls

- Not all institutions have the same 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.

Don't Miss This!

- Interpretation of liver tests requires detailed knowledge of the 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 33
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 under recognized 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

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_33

any of 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. 33.1 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. 33.1) 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

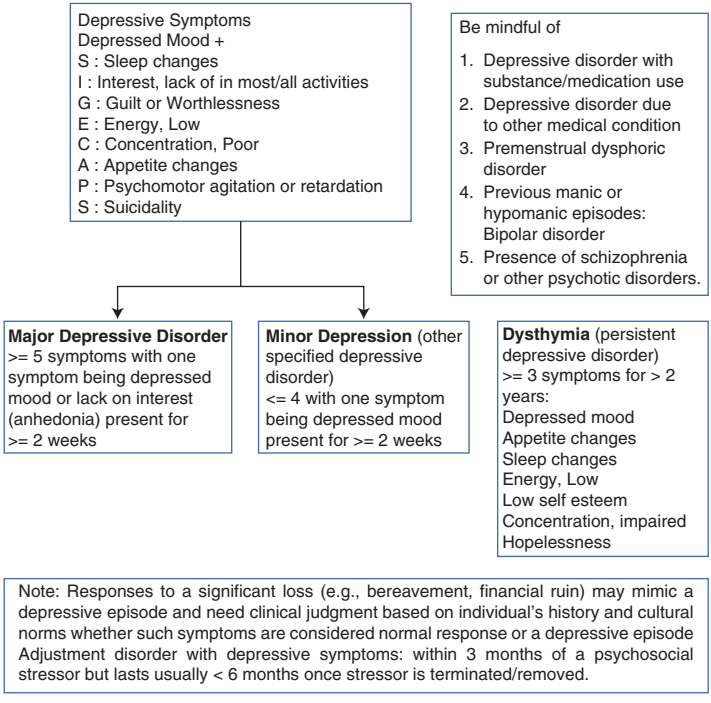

FIG. 33.1 Evaluation for syndrome of major depressive disorder

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]. 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) [11].

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 [12]. GAD typically has a gradual onset with subsyndromal anxiety common before the age of 20 years and eventual progression of anxiety in later years [13]. 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 development of coronary heart disease [14].

Patients with comorbid major depression and GAD tend to have a more severe and prolonged course of illness and greater functional impairment [15].

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 [16]. The Hospital Anxiety and Depression Scale (HADS) has the benefit of assessing and monitoring the severity of symptoms of both anxiety and depression [17]. An algorithm suggested for screening and treatment for GAD is presented in Fig. 33.2.

The US Preventive Services Task Force recommends screening all adults (age >18 years old) for depression at least once and using clinical judgment to determine whether to do additional screening for high-risk patients [18]. The PHQ-2 is a very brief, two-question instrument, which offers acceptable properties as screening tool; it should not, however, be con-

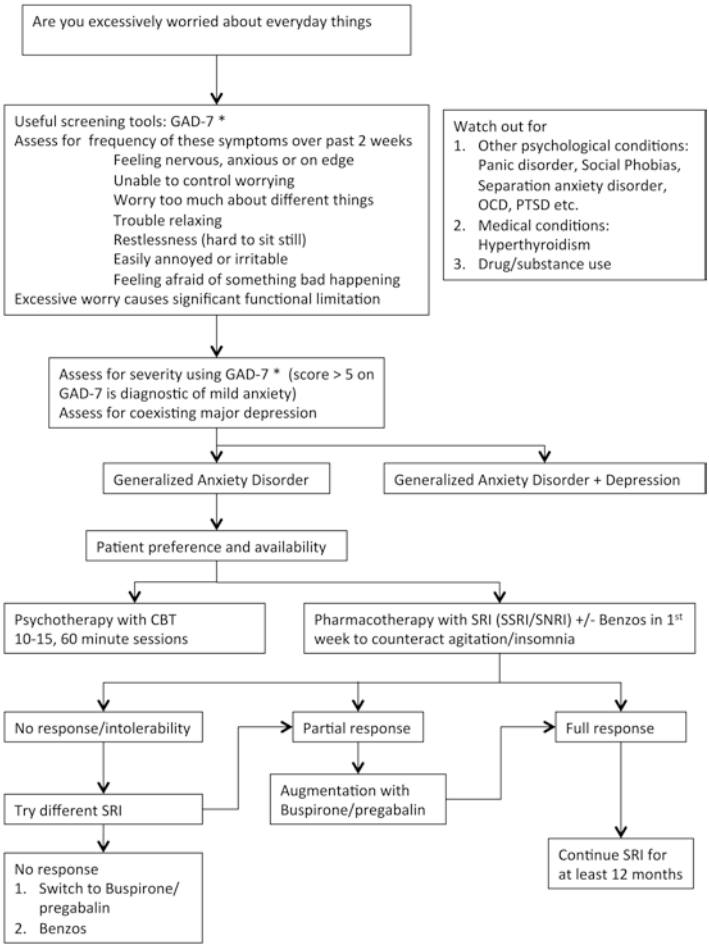

FIG. 33.2 Suggested algorithm for screening and management of generalized anxiety disorder. Reprinted with permission [23]

sidered adequate for diagnosis [19]. An algorithm for screening and treatment recommendations for major depressive disorder is shown in Fig. 33.3.

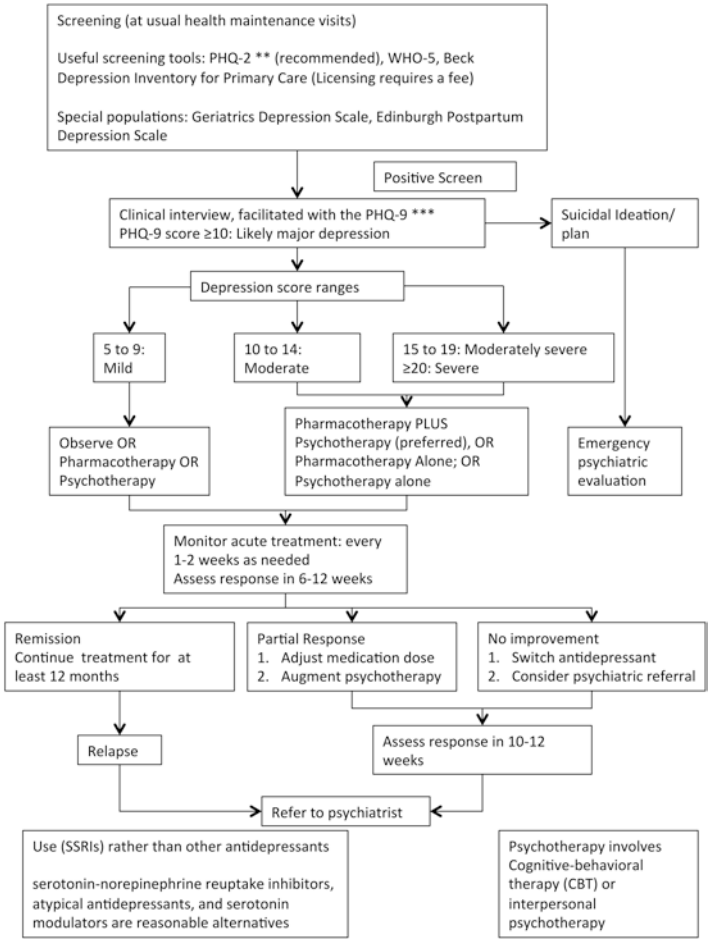

FIG. 33.3 Suggested algorithm for screening and management of major depressive disorder. Reprinted with permission [24, 25]

List of medication commonly prescribed for MDD, with their usual daily dosages and side effect profiles are listed in Table 33.1 [20].

TABLE 33.1 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

Primary GAD with secondary depressive symptoms can be difficult to distinguish from major depressive disorder or 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 [21]. 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 [22]. 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 non-depressed people. Treat depression first if the source or severity of pain is questionable.

Sleep problems and appetite changes are common in the elderly, so consider depression when hearing about these symptoms.

Don't 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 depressed patient.

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Chapter 34
Insomnia

Shadi Dowlatshahi and Aaron D. Storms

Introduction

Insomnia is one of the most common patient complaints in the ambulatory setting. It is defined as difficulty with initiating sleep (i.e., taking longer than 30 min to fall asleep), maintaining sleep (i.e., waking up more than three times per night), or waking up too early (i.e., staying asleep for fewer than 6 h) despite adequate opportunity 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, the general consensus is that about 30–50% of adults present with this complaint at some point, with about 20% having a persistent problem [2]. Risk factors for insomnia include female sex, increased

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_34

age, low socioeconomic status, unemployment, and the marital status of divorced, widowed, or separated [3–5]. Patients with comorbid medical or psychiatric conditions are at even further increased risk with rates as high as 50–75% [6–8].

Insomnia is classified as acute or chronic. Acute insomnia is defined as insomnia present for less than 1 month. It is typically caused by changes in sleep environment, stress, or severe depression and may recur when new or similar stresses present [1]. Once the patient adapts to the new stressor or it resolves, the insomnia is expected to resolve as well [1]. Chronic insomnia is defined as insomnia that persists for more than 1 month. Although once thought that all insomnia was related to a comorbid condition, it is now recognized that chronic insomnia may be either primary or comorbid. Primary chronic insomnia is diagnosed when no underlying etiology or cause for the insomnia is determined. It should be noted though that some patients may have primary insomnia in the setting of a comorbid condition [9]. Comorbid insomnia, previously referred to as secondary insomnia, may be related to a wide variety of medical and psychiatric conditions and is the most common cause of chronic insomnia.

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, and medication use, as well as having higher rates of absenteeism and work-related errors [10]. 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 to assess if insomnia is due to a medical or psychiatric condition, medication effect, or substance use.

History

Patients should be asked about their sleep history to determine the type of insomnia (i.e., issues with initiation versus maintenance), the duration (i.e., acute or chronic), and the course (i.e., recurrent or persistent). Questions regarding alleviating versus provoking factors, sleep schedule, alcohol and drug use, caffeine intake, and activities prior to bedtime should also be solicited. Examples of questions to ask patients may include [11–13]:

- How long has this problem been occurring? How has your sleep been?
- Do you wake up frequently at night? Have problems falling asleep? Have problems staying asleep?
- What kind of work hours do you have? Are you a shift worker?

Assess Sleep Hygiene:

- What time do you go to bed? Do you go to bed at the same time every night? (i.e., weekends versus weekdays); How long do you typically sleep?
- Is your sleeping environment conducive to sleep? (i.e., noise, temperature, light)
- How do you unwind before bedtime?
- Do you watch TV or read in bed prior to going to sleep?
- Do you take daytime naps?

Patients should be asked about daytime consequences of poor sleep. Common symptoms they may experience include fatigue, decreased energy, tiredness, lack of concentration, mood disturbances, and concern about sleep. The Epworth Sleepiness Scale questionnaire may be administered if a patient complains of excess daytime sleepiness, as this would indicate a different sleep disorder from insomnia [13]. 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, wake time after sleep onset, number of awakenings, any sleep aids (including medications), quality of sleep, nap times, and daytime symptoms [12]. The diary may be later used as a baseline for comparison when treatment is initiated.

Social History

Patient's alcohol, caffeine, tobacco, and drug history should be evaluated. If a patient presents with acute insomnia, questions regarding recent stressors (e.g., new job, change in location, change in relationship) should be addressed.

Medical History

A thorough review of systems and medical history should be obtained to reveal any underlying psychiatric or medical conditions that may be present. Specifically, patients should be evaluated for mood and anxiety disorders which account for the majority of psychiatric disorders causing chronic insomnia [11, 12]. Major depressive disorder may be quickly excluded if the patient responds "no" to both of the following questions: In the past 2 weeks, (1) have you felt down, depressed, or hopeless, and (2) have you had little interest or find no pleasure in doing things? [14]. Post-traumatic stress disorder is another common psychiatric etiology for insomnia.

Common medical comorbidities associated with insomnia include pulmonary disease, neurologic disease, heart failure, hypertension, diabetes, malignancy, and chronic pain [1, 15]. 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 lead to insomnia include [1, 6–8]:

- 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)
- Hormones (i.e., glucocorticoids, thyroid medication)

Withdrawal of sedatives, hypnotics, 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. Certain exam features that should be specifically addressed include obesity, neck circumference, and upper airway obstruction to diagnose sleep apnea.

Differential Diagnosis

Diagnoses to consider in the differential for insomnia include [6–8, 13]:

- Underlying psychiatric/medical condition (i.e., comorbid insomnia)
- Medication-induced insomnia
- Sleep-related breathing disorders (i.e., obstructive sleep apnea, Cheyne-Stokes breathing)
- Short duration sleep
- Chronic sleep restriction
- Movement disorders (i.e., restless leg syndrome, periodic limb movements during sleep)
- Sleeplessness and circadian rhythm disorder
- Sleep-disruptive environmental circumstances

Decision-Making

Insomnia is a clinical diagnosis and is based on sleep history. Diagnosis of insomnia includes meeting the following three criteria per the DSM-5 and International Classification of Sleep Disorders, Third Edition (ICSD-3) [1, 11]:

- Difficulty in initiating sleep, maintaining sleep, or early-morning awakenings
- Occurs despite ample opportunity for sleep
- Daytime deficits in function occur due to impaired sleep

No specific work-up is needed to diagnose insomnia; however patients should maintain a sleep journal for 1–2 weeks in order to aid in diagnosis. Further, the sleep diary may be used before and during treatment to evaluate for success.

Patients may benefit from polysomnography if there is concern for sleep apnea or for patients with suspected restless leg syndrome/periodic limb movement disorder. Actigraphy is another test modality that may help in documenting patients' sleep patterns and circadian rhythms. It works by monitoring a patient's movement. Therefore, if there is a prolonged period of no movement then the patient is considered to be sleeping, while periods of prolonged movement indicate activity. Actigraphy may be used in correlation with the sleep journal to determine length of sleep [16]. Other tests that may be beneficial include psychiatric screening tools to assess for depression and anxiety, echocardiogram, thyroid function tests, hemoglobin A1c, and iron studies.

Treatment

The goal of treatment is to improve sleep quality and daytime functioning [1]. Comorbid conditions, including medical, psychiatric, substance abuse, should all be addressed and treated, as they may be precipitating or provoking the insomnia. See Fig. 34.1.

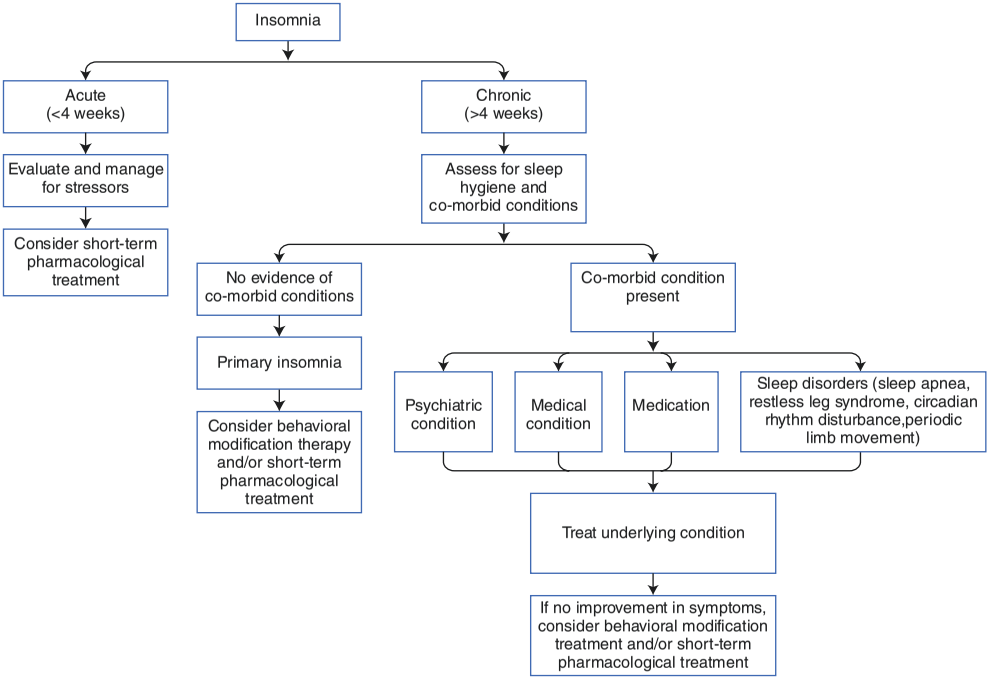

FIG. 34.1 Insomnia algorithm

The American Academy of Sleep Medicine and American College of Physicians both endorse the use of behavioral therapy, specifically cognitive behavioral therapy (CBT), as first-line treatment in chronic insomnia, regardless of primary or comorbid etiology [1, 17]. Patients who do not improve with behavioral therapy may benefit from pharmacological treatment as an adjunct or as stand-alone treatment. Patients with acute insomnia may benefit from medication as first-line treatment, as this type of insomnia is typically self-limited.

Behavioral Therapy

Behavioral therapy includes sleep hygiene education, stimulus control, relaxation, sleep restriction therapy, cognitive therapy, and CBT. Patients are initially educated about sleep hygiene and stimulus control; however, if symptoms persist then cognitive therapy and CBT may be employed. The success of treatment is based on the patient implementing the behavioral therapy.

Sleep Hygiene

Sleep hygiene consists of addressing and rectifying behaviors that are incompatible with sleep. These include avoiding caffeine, alcohol, and nicotine before bedtime, decreasing stimuli (i.e., noise, lighting), avoiding daytime naps, exercising daily, not forcing sleep, and maintaining a regular sleep schedule [13, 18, 19].

Stimulus Control

Patients undergoing stimulus control therapy are educated on associating their bed with sleeping time, as opposed to arousal time. Therefore, they are instructed to use the bed for sleeping and sexual activity purposes only [13, 19].

Relaxation Therapy

Patients are taught biofeedback techniques to help reduce tension and relax muscle groups. This therapy consists of utilizing guided imagery and meditation to help relax the patient prior to bed.

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, as it may have an effect on the circadian rhythm. Sleep restriction therapy entails limiting the time the patient spends in bed. 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 by 15–30 min every week, as the patient reports a sleep efficiency of greater than 85% (sleep efficiency = time asleep/time in bed) [13, 19].

Cognitive Therapy

As patients tend to have a lot of worrying surrounding trying to achieve sleep, with cognitive therapy, they are educated to correct their inaccurate thoughts to reduce stress and worry [13, 19].

Cognitive Behavioral Therapy

CBT involves combining the previously mentioned therapies over the course of several weeks. It has been shown to be superior to medication use in the treatment of primary insomnia, as patients with primary insomnia have been shown to have physiologic, emotional, and cognitive arousal in bed [13, 19–21]. It may also be used in patients with comorbid insomnia. The advantage of CBT is that it provides

TABLE 34.1 FDA-approved medications in the treatment of insomnia

Drug name	Dosage (mg)	Onset of action (h)	Indication	Half-life (h)	Side effects
Benzodiazepine receptor agonists					
Benzodiazepines					
Estazolam	1–2	0.5–1	Sleep maintenance	10–24	Daytime sleepiness
Temazepam	7.5–30	0.5–1	Sleep maintenance	8–15	Daytime sleepiness
Triazolam	0.125–0.25	0.25–0.5	Sleep onset	2–5	Anterograde amnesia, rapid eye movement sleep rebound, rebound anxiety
Non-benzodiazepines					
Zaleplon	5–15	0.5	Sleep onset	1	Altered color perception
Zolpidem	5–10	0.5	Sleep onset	2–3	Abdominal pain, rebound insomnia
Zolpidem Controlled Release	6.25–-12.5	0.5	Sleep onset or sleep maintenance	1.5–4.5	
Eszopiclone	1–3	1	Sleep onset or sleep maintenance	6–9	Unpleasant taste, amnesia, hallucinations, worsening depression

Melatonin receptor agonist					
Ramelteon	8–16	0.3	Sleep onset	2–5	Suicidal ideation, dizziness, headache, prolactinemia
Orexin receptor antagonists					
Suvorexant	10–20	0.5	Sleep onset or sleep maintenance	12	Suicidal ideation, hallucinations, amnesia
Antidepressants					
Doxepin	3–6	–	Sleep maintenance	15	QT prolongation, arrhythmias, tardive dyskinesia, hallucinations, anticholinergic symptoms

patients with the tools to improve their sleep quality; however, it is limited by the amount of time required (several 20–40-min sessions over the course of 6 weeks) and the lack of clinicians trained in CBT. The effects of CBT may be sustained for months after completion of sessions [22].

Medications

Patients whose chronic symptoms do not improve with behavioral therapy and those with acute insomnia may benefit from pharmacological treatment. Decisions regarding which pharmacological agent to prescribe include characteristics of insomnia (i.e., sleep onset versus sleep maintenance), duration of effect, patient preference, cost, prior treatment responses, comorbid conditions, and drug interactions [19]. FDA-approved medications for use in the treatment of insomnia include benzodiazepine receptor agonists (BDZRA), melatonin agonists, doxepin, and suvorexant (Table 34.1). There are few clinical trials comparing the efficacy of these medications to one another; however, no significant difference has been found [23].

Short-/intermediate-acting BDZRA or ramelteon should be used as first line. As previously mentioned, the choice of drug depends on several factors. For instance, zaleplon or ramelteon may be preferred in patients with difficulty initiating sleep, given their shorter half-lives, compared to using eszopiclone or temazepam, which may be preferred in those with difficulty maintaining sleep, given their longer half-lives. Triazolam is no longer used as a first line because of associated rebound anxiety. Some patients may prefer to use ramelteon, as it is not a controlled substance [19]. If a patient does not respond to the initial medication, or has complaints of side effects, a different drug from the same class may be utilized [19]. Patients who fail treatment with BDZRA or ramelteon or who have comorbid depression may benefit from low-dose sedating antidepressants including trazodone, mirtazapine, doxepin, amitriptyline, or trimipramine [19]. Data are insufficient to support the use of several other medi-

cations that are used off-label in the treatment of insomnia, including gabapentin, tiagabine, quetiapine, and olanzapine. Over-the-counter agents such as antihistamines may be used as self-remedies; however, they have the potential for serious side effects including anticholinergic symptoms. Herbal supplements such as valerian and melatonin have been shown to have a small benefit in the treatment of insomnia [19].

There are no specific guidelines regarding the dosing frequency in which these pharmacological agents should be used. Some physicians will recommend nightly use, while others recommend intermittent use to prevent tolerance, abuse, and dependence. Minimal treatment time is 2–4 weeks before deciding to continue with treatment or to change the treatment regimen. Similar to dosing frequency, there are no guidelines regarding length of treatment. If patients are using BDZRA for long periods of time they should be monitored frequently for efficacy, side effects, tolerance, abuse and/or dependence, and attempts should be made to decrease the dose and frequency [19].

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 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 medical/psychiatric evaluation to determine underlying etiology and should maintain a sleep diary for 2 weeks as part of the diagnostic evaluation for insomnia.
- 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. If these are ineffective then pharmacologic methods are recommended. Medications may be used as first-line treatment of acute insomnia as this tends to be self-limited.

Don't Miss This!

- Insomnia is a clinical diagnosis and is typically associated with an underlying psychiatric or medical condition, so be certain to rule out underlying conditions before proceeding to treat insomnia!

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Chapter 35
Memory Loss/Cognitive Impairment

Jarrod A. Carrol and Zaldy S. Tan

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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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9_35

Key History and Physical Exam/Decision-Making

While the United States Preventive Services Task Force (USPSTF) does not currently recommend routine screening of asymptomatic patients for cognitive impairment (2014 USPSTF 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 *nature* 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 his/her usual level of cognitive functioning?
- What is the *Course* 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 (*ADLs*)/instrumental activities of daily living (IADLs)? (see Chap. 3)
  - Be sure to differentiate between functional decline secondary to cognitive impairment from 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 regarding onset of memory loss and type/extent of deficits. In some cases these key contributors may be the initial source of information when patients 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 Patient Health Questionnaire (PHQ) and the Geriatric Depression Scale (GDS). 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 his/her 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 are validated tools that are easily used in a primary care setting (Table 35.1).

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 imaging completed in the primary care setting. It provides a general view of brain anatomy. It can detect generalized atrophy, space-occupying lesions, and previous large territory infarcts and can 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 Alzheimer's Disease), white matter changes, and smaller infarcts (i.e., vascular dementia, mixed dementia).

TABLE 35.1 Cognitive screening tools

Screening tool	Time to administer	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

(continued)

TABLE 35.1 (continued)

Screening tool	Time to administer	Domains tested	Scoring	Sensitivity/specificity in detecting dementia	Advantages (A)/ disadvantages (D)
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 (minimal cognitive impairment) and difficulty detecting changes in severe dementia
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 in diagnosing MCI. Available in multiple languages D: time to administer so usually not done in primary care

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 update by parts of brain (decreased uptake in temporal and parietal areas in AD and decreased uptake in frontal and temporal areas in frontotemporal dementia).

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 incomplete resolution of memory symptoms.
- Hypothyroidism
  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 impairment. 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–drug interactions may result in forgetfulness or confusion.
- Mild Cognitive Impairment (MCI)
  MCI is noted as mild neurocognitive disorder in DSM-V [16]. With MCI, there is 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. Patient 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 (Table 35.2)

Treatment

Medications (Table 35.3)

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.

Don't 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.

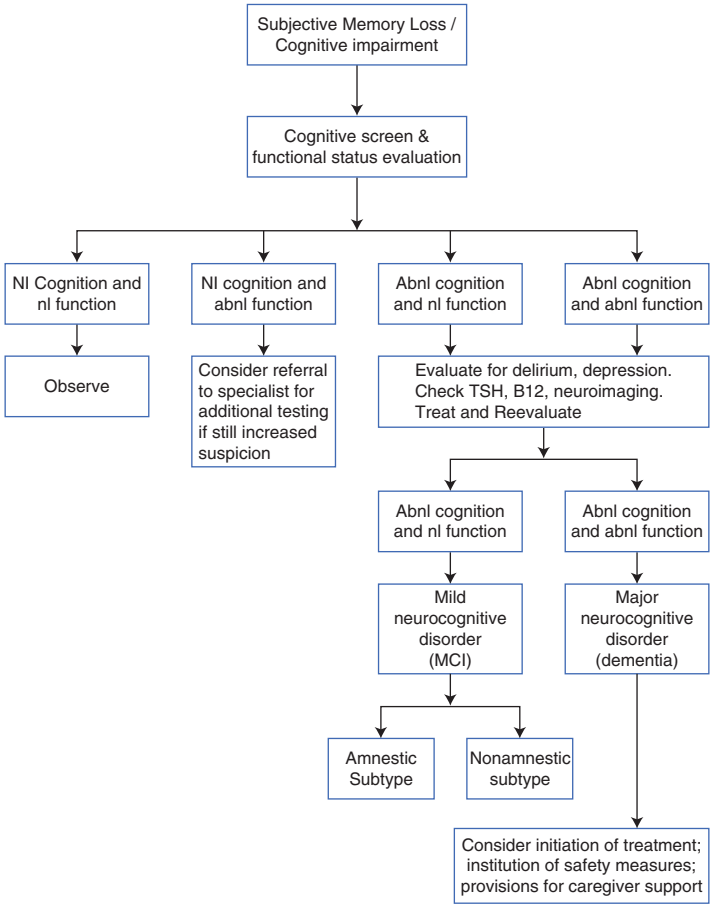

FIG. 35.1 Memory loss evaluation algorithm

– 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 Parkinson's disease, dementia, and Lewy body dementia).

TABLE 35.2 Dementia (DSM-5: major neurocognitive disorder [16])

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 slowly progressive with small vessel disease	Ischemic, hemorrhagic, or hypoxic lesions
Parkinson's dementia	Typically have features of parkinsonism	Parkinson's disease for many years prior to onset of cognitive decline	Neuronal loss in the substantia nigra
Lewy body dementia	Typically patients have visual hallucinations, REM sleep behavior disorders early in course	Cognitive complaints appear before or around same time as movement disorder symptoms	Lewy bodies
Frontotemporal dementia (FTD)	Typically earlier onset (<65 years old)	Marked personality changes. Multiple forms including behavioral variant, semantic, progressive nonfluent aphasia, and FTD with motor neuron disease	Tau protein

Other less common forms: alcohol-related dementia, HIV dementia, Prion/Creutzfeldt–Jakob disease, Huntington's disease

TABLE 35.3 Medications

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] daily) for 4 weeks, titrate to 8 mg BID (or 16 mg ER daily long-acting) for 4 weeks, then 12 mg twice daily (or 24 mg ER daily long-acting) Rivastigmine—1.5 mg BID for 4 weeks, titrate to 3 mg twice daily for 4 weeks, then 4.5–6 mg twice daily *or* rivastigmine (Exelon) transdermal 4.6 mg/24 h patch daily for 4 weeks, titrate to 9.5 mg/24 h daily patch, then 13.3 mg/24 h daily patch	Gastrointestinal intolerance (nausea, vomiting, diarrhea, anorexia), bradycardia, and vivid dreams
NMDA-receptor antagonist	Blocks glutamate at NMDA-receptor	Memantine—Start 5 mg daily for 1 week, then 5 mg twice daily for 1 week, then 10 mg every morning and 5 mg at bedtime for 1 week, and then 10 mg twice daily *or* Memantine (Namenda) XR 7 mg every AM for 1 week increasing by 7 mg/week to max dose of 28 mg every AM	Confusion, drowsiness

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E. Sydney et al. (eds.), *Handbook of Outpatient Medicine*,
https://doi.org/10.1007/978-3-319-68379-9