Common Symptoms

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=== COUGH ===

>» Age, duration of cough, occupational history, environmental exposures, and risk of infection with SARS-CoV-2.

> Use of tobacco, cannabis, e-cigarettes (vaping).

> Dyspnea (at rest or with exertion).

> Vital signs (heart rate, respiratory rate, body temperature); pulse oximetry.

>» Chest examination.

> CXR, especially when unexplained cough lasts

> 3-6 weeks.

General Considerations

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

Clinical Findings

A. Symptoms

Distinguishing acute (less than 3 weeks), persistent (3-8 weeks), and chronic (more than 8 weeks) cough illness syndromes is a useful first step in evaluation. Postinfectious cough lasting 3-8 weeks has also been referred to

as subacute cough to distinguish this common, distinct clinical entity from acute and chronic cough.

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

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

approaches 20% (although its exact prevalence is difficult to ascertain due to the limited sensitivity of diagnostic tests).

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

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

B. Physical Examination

Pneumonia is suspected when acute cough is accompanied

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

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

C. Diagnostic Studies

1. Acute cough—CXR should be considered for any adult with acute cough whose vital signs are abnormal or whose chest examination suggests pneumonia. The relationship between specific clinical findings and the probability of pneumonia is shown in Table 2-1. A large, multicenter randomized study found that elevated serum CRP (greater than 30 mg/dL) improves diagnostic accuracy of clinical prediction rules for pneumonia in adults with acute cough;

serum procalcitonin had only marginal utility in outpatient management (in contrast with severe pneumonia requiring hospital care). A meta-analysis found that lung ultrasonography had better accuracy than CXR for the diagnosis of adult community-acquired pneumonia. In patients with dyspnea, pulse oximetry and peak flow help exclude hypoxemia or obstructive airway disease. However, a normal pulse oximetry value (eg, greater than 93%) does not rule out a significant alveolar-arterial (A-a) gradient when patients have effective respiratory compensation.

2. Persistent and chronic cough—CXR is indicated when ACE inhibitor therapy-related and postinfectious cough are

Table 2-1. Positive and negative LRs of history, physical examination, and laboratory findings in the diagnosis of pneumonia.

Finding	Positive LR	Negative LR
Medical history		
Fever	1.7-2.1	0.6-0.7
Chills	13-17	0.7-0.9
Physical examination		
Tachypnea (respiratory rate > 25 breaths/min)	1.5-3.4	0.8
Tachycardia (> 100 beats/min in two studies or > 120 beats/min in one study)	1.6-2.3	0.5-0.7
Hyperthermia (> 37.8°C)	14-44	0.6-0.8
Chest examination		
Dullness to percussion	2.2-4.3	0.8-0.9
Decreased breath sounds	2.3-2.5	0.6-0.8
Crackles	1.6-2.7	0.6-0.9

Rhonchi 1.4-1.5 0.8-0.9

Egophony 2.0-8.6 0.8-1.0

Laboratory findings

Leukocytosis (> 11,000/mcL 1.9-3.7 0.3-0.6

[11 x 10°/L] in one study or

= 10,400/mcL [10.4 x 10°/L]

in another study)

excluded. If pertussis is suspected, PCR testing should be performed on a nasopharyngeal swab or nasal wash specimen—although the ability to detect pertussis decreases as the duration of cough increases. When the chest film is normal, postnasal drip, asthma, or GERD are the most likely causes. The presence of typical symptoms of these conditions directs further evaluation or empiric therapy, though typical symptoms are often absent. Definitive tests for determining the presence of each are available (Table 2-2). However, empiric treatment with a maximum-strength regimen for postnasal drip, asthma, or GERD for 2-4 weeks is one recommended approach since documenting the

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

Suspected

Condition

Step 1

(Empiric Therapy)

Step 2

(Definitive Testing)

Postnasal drip Therapy for allergy or

chronic sinusitis

Sinus CT scan; otolaryn-

gologic referral

Asthma Beta-2-agonist Spirometry; consider
methacholine
challenge if normal
GERD Lifestyle and diet Esophageal pH
modifications with monitoring
or without PPIs

=== COMMON SYMPTOMS ===

presence of postnasal drip, asthma, or GERD does not mean they are the cause of the cough. Alternative approaches to identifying corticosteroid-responsive cough due to asthma include examining induced sputum for increased eosinophil counts (greater than 3%) or providing an empiric trial of prednisone, 30 mg daily orally for 2 weeks. Nonasthmatic eosinophilic bronchitis can be diagnosed by finding eosinophils with induced sputum analysis after the exclusion of other causes for chronic cough by clinical, radiologic, and lung function assessment. 'The cough usually responds well to inhaled corticosteroids.

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

Differential Diagnosis

A. Acute Cough

Acute cough may be a symptom of acute respiratory tract

infection, COVID-19, asthma, allergic rhinitis, HE, and ACE inhibitor therapy, as well as many less common causes.

When community influenza-like illness activity levels are high, clinical diagnosis of influenza (cough, fever, chills with or without sweats, myalgias, and acute onset) has a positive predictive value of approximately 70%; this usually obviates the need for rapid diagnostic tests to guide isolation and empiric treatment decisions. The CDC's FluView displays weekly updates of influenza surveillance data (https://www.cdc.gov/flu/weekly/index.htm).

B. Persistent and Chronic Cough

Causes of persistent cough include environmental exposures (cigarette smoke, air pollution), occupational exposures, pertussis, postnasal drip, asthma (including cough-variant asthma), GERD, COPD, chronic aspiration, bronchiectasis, nonasthmatic eosinophilic bronchitis, tuberculosis or other chronic infection, interstitial lung disease, and bronchogenic carcinoma. The prevalence of cough 1 year after hospitalization for COVID-19 is 2.5%. COPD is a common cause of persistent cough among patients older than 50 years who have smoked cigarettes. Persistent cough may also be due to somatic cough syndrome or tic cough, or vocal fold dysfunction. When empiric treatment trials fail, consider other causes of chronic cough such as obstructive sleep apnea, tonsillar or uvular enlargement, and environmental fungi (see Chapter 38).

C. Cough in the Immunocompromised Patient

The evaluation of cough in immunocompromised patients is the same as in immunocompetent patients but with an

increased concern for tuberculosis (regardless of radiographic findings) as well as fungi, cytomegalovirus, varicella, herpesvirus, and Pneumocystis jirovecii.

Treatment

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

When influenza is diagnosed, oral oseltamivir or zanamivir or intravenous peramivir are equally effective (1 less day of illness) when initiated within 30-48 hours of illness onset; treatment is recommended regardless of illness duration when patients have severe, complicated, or progressive influenza and in patients requiring hospitalization.

In Chlamydophila- or Mycoplasma-documented infection or outbreaks, first-line antibiotics include erythromycin or doxycycline. Antibiotics do not improve cough severity or duration in patients with uncomplicated acute bronchitis.

In patients with bronchitis and wheezing, inhaled beta-2-agonists reduce severity and duration of cough. In patients with acute cough, treating the accompanying post-nasal drip (with antihistamines, decongestants, saline nasal irrigation, or nasal corticosteroids) can be helpful. Two studies found codeine to be no more effective than placebo in reducing acute cough symptoms.

Evaluation and management of persistent cough often require multiple visits and therapeutic trials, which frequently lead to frustration, anger, and anxiety. When per-

tussis infection is suspected early in its course, treatment with a macrolide antibiotic (see Chapter 35) is appropriate to reduce organism shedding and transmission. When pertussis has lasted more than 7-10 days, antibiotic treatment oes not affect the duration of cough, which can last up to 6 months. Early identification, revaccination with Tdap, and treatment are encouraged for adult patients who work or live with persons at high risk for complications from pertussis (pregnant women, infants [particularly younger than 1 year], and immunosuppressed individuals).

Table 2-2 outlines empiric treatments for persistent cough. There is no evidence to guide how long to continue treatment for persistent cough due to postnasal drip, asthma, or GERD. Studies have not found a consistent benefit of inhaled corticosteroid therapy in adults with There is insufficient evidence to recommend the routine use of any pharmacologic treatments (antibiotics, bronchodilators, mucolytics) to relieve chronic cough due to stable chronic bronchitis.

The small percentage of patients with idiopathic chronic cough should be managed in consultation with an otolaryngologist or a pulmonologist; consider a high-resolution CT scan of the lungs. Treatment options include lidocaine throat spray, nebulized lidocaine therapy, and morphine sulfate, 5-10 mg orally twice daily. Sensory dysfunction of the laryngeal branches of the vagus nerve may contribute to persistent cough syndromes and may explain the effectiveness of gabapentin and baclofen in patients with chronic cough.

Speech pathology therapy combined with pregabalin has some benefit in chronic refractory cough. In patients

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

When to Refer

« Failure to control persistent or chronic cough following empiric treatment trials.

« Patients with recurrent symptoms should be referred to an otolaryngologist, pulmonologist, or gastroenterologist.

When to Admit

« Patient at high risk for tuberculosis for whom compliance with respiratory precautions is uncertain.

« Need for urgent bronchoscopy, such as suspected foreign body.

« Smoke or toxic fume inhalational injury.

* Gas exchange is impaired by cough.

+ Patients at high risk for barotrauma (eg, recent pneumothorax).

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=== DYSPNEA ===

> Fever, cough, risk of COVID-19 infection, and chest pain.
> Vital sign measurements; pulse oximetry.
Cardiac and chest examination.
>» CXR and ABG measurement in selected patients.
Dyspnea is a subjective experience or perception of uncomfortable breathing. The relationship between level of dyspnea and the severity of underlying disease varies widely. Dyspnea can result from conditions that increase the mechanical effort of breathing (eg, asthma, COPD, restrictive lung disease, respiratory muscle weakness), alveolar lung disease (pulmonary edema, pneumonia, alveolar proteinosis), conditions that produce compensatory tachypnea (eg, hypoxemia, acidosis), primary pulmonary vasculopathy (pulmonary hypertension), or psychogenic conditions. The duration, severity, and periodicity of dyspnea influence the tempo of the clinical evaluation. Rapid onset or severe dyspnea in the absence of other clinical features should raise concern for PE, increased LVEDP, or pneumothorax.
PE should always be suspected when a patient with new dyspnea reports a recent history (previous 4 weeks) of prolonged immobilization or surgery, estrogen therapy, or other risk factors for DVT (eg, previous history of throm-

boembolism, cancer, obesity, lower extremity trauma) and when the cause of dyspnea is not apparent. Silent MI, which occurs more frequently in persons with diabetes and women, can result in increased LVEDP, acute HE, and dyspnea. Spontaneous pneumothorax is usually accompanied by chest pain and occurs most often in thin, young men and in those with underlying lung disease.

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

When a patient reports prominent dyspnea with mild or no accompanying features, consider chronic PE and noncardiopulmonary causes of impaired oxygen delivery (anemia, methemoglobinemia, cyanide ingestion, carbon

monoxide poisoning), metabolic acidosis, panic disorder, and neuromuscular disorders.

The diagnosis of heart failure with preserved ejection fraction (HFpEF) as the cause of dyspnea is challenging in the absence of overt congestion; the diagnosis may be made by echocardiography.

Patients who recover from their initial COVID-19 infection may have persistent dyspnea as part of the "long COVID" syndrome. Platypnea-orthodeoxia syndrome is characterized by dyspnea and hypoxemia on sitting or standing that improves in the recumbent position.

Hyperthyroidism can cause dyspnea from increased ventilatory drive, respiratory muscle weakness, or pulmonary hypertension.

A focused physical examination should include evaluation of the head and neck, chest, heart, and lower extremities. Visual inspection of the patient can suggest obstructive airway disease (pursed-lip breathing, use of accessory respiratory muscles, barrel-shaped chest), pneumothorax (asymmetric excursion), or metabolic acidosis (Kussmaul respirations). Patients with impending upper airway obstruction (eg, epiglottitis, foreign body) or severe asthma exacerbation sometimes assume a tripod position. Focal wheezing raises the suspicion for a foreign body or other bronchial obstruction.

Maximum laryngeal height (the distance between the top of the thyroid cartilage and the suprasternal notch at end expiration) is a measure of hyperinflation. Obstructive airway disease is virtually nonexistent when a nonsmoking patient younger than age 45 years has a maximum laryngeal height greater than 4 cm; factors increasing the likeli-

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

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

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

Causes of dyspnea that can be managed without CXR are few: anemia, carbon monoxide poisoning, and ingestions causing lactic acidosis and methemoglobinemia.

1. Chest radiography—The diagnosis of pneumonia should be confirmed by CXR in most patients, and elevated blood levels of procalcitonin or CRP can support the diagnosis of pneumonia in equivocal cases or in the presence of interstitial lung disease. Conversely, a low procalcitonin can help exclude pneumonia in dyspneic patients presenting with HF (see Table 2-1 for other diagnostic findings in pneumonia).

CXR has a moderate sensitivity (53-75%) and a high

specificity (86-96%) for new-onset HF (represented by redistribution of pulmonary venous circulation) and can help guide treatment of patients with other cardiac diseases. NT-proBNP can assist in the diagnosis of HF (see below). End-expiratory CXR enhances detection of small pneumothoraces. A normal CXR has substantial diagnostic value. When there is no physical examination evidence of COPD or HF and the CXR is normal, the major remaining causes of dyspnea include PE, P jirovecii infection (the initial radiograph may be normal in up to 25%), upper airway obstruction, foreign body, anemia, and metabolic acidosis. If a patient has tachycardia or hypoxemia but a normal CXR and ECG, then tests to exclude pulmonary emboli, anemia, or metabolic acidosis are warranted.

2. Point-of-care ultrasonography (POCUS)—A systematic review of five RCTs and 44 prospective cohort-type studies in patients with acute dyspnea assessed POCUS as a diagnostic tool to determine the underlying cause of dyspnea. When added to a standard diagnostic pathway, POCUS led to statistically significantly more correct diagnoses in patients with dyspnea than the standard diagnostic pathway. POCUS consistently improved the sensitivities of standard diagnostic pathways to detect HE, pneumonia, PE, pleural effusion, or pneumothorax. Specificities increased in most studies; in-hospital mortality and length of hospital stay, however, did not differ significantly between patients who did or did not receive POCUS in addition to standard diagnostic tests.

3. High-resolution chest CT—This test is particularly useful in the evaluation of interstitial and alveolar lung disease. Helical (“spiral”) CT is useful to diagnose PE since the

images are high resolution and require only one breath hold by the patient, but to minimize unnecessary testing and radiation exposure, the clinician should first employ a clinical decision rule for ruling out acute PE, such as the PERC (Pulmonary Embolism Rule-Out Criteria) the Wells score, the revised Geneva scores with fixed or adapted D-dimer thresholds, or the YEARS algorithm. It is appropriate to forego CT scanning in patients with low probability of pulmonary embolus when other causes of dyspnea are more likely (see Chapter 9).

4. Pulmonary function testing with diffusing capacity of the lungs for carbon monoxide—A low D1co is associated with interstitial lung disease, emphysema, pulmonary vascular disease, chronic HF, and drug toxicity. A Dico above the upper limit of normal (uncommon) may occur in individuals with asthma, obesity, or increased blood volume or hemoglobin (polycythemia, left-to-right cardiac shunt, pregnancy, pulmonary hemorrhage).

5. Cardiopulmonary exercise testing—A maximal exercise test with a gas exchange analysis that determines minute ventilation, heart rate, oxygen uptake, and carbon dioxide output. It may help determine the cause of exertional dyspnea, exercise intolerance, or exercise-induced hypoxemia.

6. Serum BNP and cardiac troponin—Laboratory findings suggesting increased LVEDP include elevated serum BNP or NT-proBNP levels. High-sensitivity cardiac troponin T (hs-CTnT) may be a marker of HFpEF causing dyspnea. BNP has been shown to reliably diagnose severe dyspnea caused by HF and to differentiate it from dyspnea due to other conditions.

7. Arterial blood gas—ABG measurement may be consid-

ered if clinical examination and routine diagnostic testing are equivocal. With two notable exceptions (carbon monoxide poisoning and cyanide toxicity), ABG measurement distinguishes increased mechanical effort causes of dyspnea (respiratory acidosis with or without hypoxemia) from compensatory tachypnea (respiratory alkalosis with or without hypoxemia or metabolic acidosis) and from psychogenic dyspnea (respiratory alkalosis). Carbon monoxide and cyanide impair oxygen delivery with minimal alterations in Po,; percent carboxyhemoglobin identifies carbon monoxide toxicity. Cyanide poisoning should be considered in a patient with profound lactic acidosis following exposure to burning vinyl (such as a theater fire or industrial accident). Suspected carbon monoxide poisoning or methemoglobinemia can also be confirmed with venous carboxyhemoglobin or methemoglobin levels. Venous blood gas testing is also an option for assessing acid-base and respiratory status by measuring venous pH and Pco, but is unable to provide information on oxygenation status. To correlate with ABG values, venous pH is typically 0.03—-0.05 units lower, and venous Pco, is typically 4—5 mm Hg higher than arterial samples.

8. Pulse oximetry—Because ABG testing is impractical in most outpatient settings, pulse oximetry is useful in the office evaluation of dyspnea. Oxygen saturation values above 96% almost always correspond with a Po, greater than 70 mm Hg, whereas values less than 94% may represent clinically significant hypoxemia. Important exceptions to this rule include carbon monoxide toxicity, which leads to a normal oxygen saturation (due to the similar wavelengths of oxyhemoglobin and carboxyhemoglobin), and

methemoglobinemia, which results in an oxygen saturation of about 85% that fails to increase with supplemental oxygen. Pulse oximetry to detect occult hypoxia is less accurate in Black patients (OR, 2.57) compared to White patients. A delirious or obtunded patient with obstructive lung disease warrants immediate measurement of ABGs to exclude hypercapnia and the need for intubation, regardless of the oxygen saturation. If a patient reports dyspnea with exertion, but resting oximetry is normal, assessment of desaturation with ambulation (eg, a brisk walk around the clinic) can be useful for confirming impaired gas exchange. Persons with COVID-19 may have low oxygen saturation with minimal dyspnea and profound desaturation with minimal exertion.

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

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

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

The treatment of urgent or emergent causes of dyspnea should aim to relieve the underlying cause. Pending diagnosis, patients with hypoxemia should immediately be provided supplemental oxygen unless significant hypercapnia is strongly suspected pending ABG measurement. In the management of acute respiratory failure, high-flow nasal oxygen may reduce all-cause mortality, rates of intubation, and hospital-acquired pneumonia compared to noninvasive ventilation. Dyspnea frequently occurs in patients nearing the end of life. Opioid therapy, anxiolytics, and corticosteroids can provide substantial relief independent of the severity of hypoxemia. Inhaled opioids are not effective.

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

« Following acute stabilization, patients with advanced COPD should be referred to a pulmonologist, and patients with HF or valvular heart disease should be referred to a cardiologist.

* Cyanide toxicity or carbon monoxide poisoning should be managed in conjunction with a toxicologist.

+ Lung transplantation can be considered for patients with advanced interstitial lung disease.

> When to Admit

« Impaired gas exchange from any cause or high risk of PE pending definitive diagnosis.

+ Suspected cyanide toxicity or carbon monoxide poisoning.

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=== HEMOPTYSIS ===

» Fever, cough, and other symptoms of lower respiratory tract infection.
> Smoking history.
Nasopharyngeal or GI bleeding.
> CXR and CBC (and, in some cases, INR).
Hemoptysis is the expectoration of blood that originates below the vocal folds. It is commonly classified as trivial, mild, or massive—the latter defined as more than 200-600 mL (about 1-2 cups) in 24 hours. Massive hemoptysis can be usefully defined as any amount that is hemodynamically significant or threatens ventilation. Its in-hospital mortality was 6.5% in one study. The initial goal of management of massive hemoptysis is therapeutic, not diagnostic.
The causes of hemoptysis can be classified anatomically. Blood may arise from the upper airway due to malignant invasion or foreign body; from the airways in COPD, bronchiectasis, bronchial Dieulafoy disease, and bronchogenic carcinoma; from the pulmonary vasculature in LV failure, mitral stenosis, PE, pulmonary arterial hypertension, telangiectasias, arteriovenous malformations, and multiple pulmonary artery aneurysms; from the systemic circulation in intralobar pulmonary sequestration, aortobronchial

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

Blood-tinged sputum in the setting of an upper respiratory tract infection in an otherwise healthy, young (age under

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

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

Diagnostic evaluation should include a CXR and CBC. Kidney function tests, UA, and coagulation studies are appropriate in specific circumstances. Hematuria that accompanies hemoptysis may be a clue to anti-basement membrane antibody disease or vasculitis. Flexible bronchoscopy reveals endobronchial cancer in 3-6% of patients with hemoptysis who have a normal (non-lateralizing) CXR. Nearly all these patients are cigarette smokers over the age of 40, and most will have had symptoms for more than 1 week. High-resolution chest CT scan complements

bronchoscopy; it can visualize unsuspected bronchiectasis and arteriovenous malformations and will show central endobronchial cancers in many cases. It is the test of choice for suspected small peripheral malignancies. Helical pulmonary CT angiography is the initial test of choice for evaluating patients with suspected PE, although caution should be taken to avoid large contrast loads with even mild CKD (serum creatinine greater than 2.0 g/dL or rapidly rising creatinine in normal range). Helical CT scanning can be avoided in patients who are at "unlikely" risk for PE using the Wells score or PERC (Pulmonary Embolism Rule-Out Criteria) rule for PE and the sensitive D-dimer test (see Chapter 9). Echocardiography may reveal evidence of HF or mitral stenosis. Multidetector CT angiography is the study of choice to determine the location, etiology, and mechanism of the bleeding.

> Treatment

Management of mild hemoptysis consists of identifying and treating the specific cause. Massive hemoptysis is life-threatening. The airway should be protected with endotracheal intubation, ventilation ensured, and effective circulation maintained. If the location of the bleeding site is known, the patient should be placed in the decubitus position with the involved lung dependent. Uncontrollable hemorrhage warrants rigid bronchoscopy and surgical consultation. In stable patients, flexible bronchoscopy may localize the site of bleeding, and angiography can embolize the involved bronchial arteries. Embolization is effective initially in 85% of cases, although rebleeding may occur in up to 20% of patients during the following year. The anterior spinal artery arises from the bronchial artery in up to

5% of people, and paraplegia may result if it is inadvertently cannulated and embolized.

One double-blind, RCT compared treatment with inhalations of tranexamic acid (an antifibrinolytic drug) versus placebo (normal saline) in patients hospitalized with mild hemoptysis (less than 200 mL of expectorated blood per 24 hours). The study findings included faster resolution of bleeding, shorter length of hospital stay, and fewer invasive procedures with tranexamic acid treatment. Decreased in-hospital mortality was observed in a separate randomized trial (11.5% mortality rate in control group versus 9.0% in patients who received tranexamic acid).

)»> When to Refer

« Refer to a pulmonologist when bronchoscopy of the lower respiratory tract is needed.

« Refer to an otolaryngologist when an upper respiratory tract bleeding source is identified.

+ Refer to a hematologist when severe coagulopathy complicates management.

* To stabilize bleeding in patients at risk for or experiencing massive hemoptysis.

¢ To correct disordered coagulation (using clotting factors or platelets, or both) or to reverse anticoagulation.

« To stabilize gas exchange.

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=== CHEST PAIN ===

> Pain onset, character, location/size, duration, periodicity, and exacerbators; shortness of breath.
> Vital signs; chest and cardiac examinations.
» ECG and biomarkers of myocardial necrosis in selected patients.
> General Considerations
Chest pain (or chest discomfort) can occur as a result of cardiovascular, pulmonary, pleural, or musculoskeletal disease; esophageal or other GI disorders; herpes zoster; cocaine use; or anxiety states. The frequency and distribution of life-threatening causes of chest pain, such as ACS, pericarditis, aortic dissection, vasospastic angina, PE, pneumonia, and esophageal perforation, vary substantially between clinical settings.
SLE, rheumatoid arthritis, reduced eGFR, and HIV infection are conditions that confer a strong risk of CAD. Precocious ACS (occurring in patients aged 35 years or younger) may represent acute thrombosis independent of underlying atherosclerotic disease. Risk factors for precocious ACS are obesity, familial hypercholesterolemia, and cigarette use.
Although ACS presents with a broader range of symptoms in women than men, specific chest pain characteristics of acute MI do not differ in frequency or strength between men and women.
Because PE can present with a wide variety of symp-

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

> Clinical Findings

Myocardial ischemia is usually described as a dull, aching sensation of “pressure,” “tightness, “squeezing,” or “gas,” rather than as sharp or spasmodic. Chest discomfort at rest is the most common presenting symptom of ACS, reported by 79% of men and 74% of women with ACS. Pain reaching maximum intensity in seconds is uncommon. Ischemic symptoms usually subside within 5-20 minutes but may last longer. Progressive symptoms or symptoms at rest may represent unstable angina. Up to one-third of patients with acute MI do not report chest pain. Chest pain is present in more than 90% of patients having a STEMI who are under age 65 but in only 57% of patients having a STEMI who are over age 85.

Continuous chest pain lasting 24 hours or longer is unlikely to be due to an acute MI (LR, 0.15). However, chest pain lasting 1 minute or less does not exclude MI (LR, 0.95). When present, pain due to myocardial ischemia is commonly accompanied by a sense of anxiety or uneasiness. The location is usually retrosternal or left precordial. Because the heart lacks somatic innervation, precise localization of pain due to cardiac ischemia is difficult; the pain is commonly referred to the throat, lower

jaw, shoulders, inner arms, upper abdomen, or back. Ischemic pain may be precipitated or exacerbated by exertion, cold temperature, meals, stress, or combinations of these factors and is usually relieved by rest. However, many episodes do not conform to these patterns, and a broader range of symptoms of ACS are more common in older adults, women, and persons with diabetes mellitus. Other symptoms that are associated with ACS include shortness of breath; dizziness; a feeling of impending doom; and vagal symptoms, such as nausea and diaphoresis. In older persons, unusual or unexplained fatigue is a common presenting complaint of ACS.

The presenting symptoms of acute MI in patients aged 18-55 (average age 47) are different in men and women. The VIRGO study of this younger cohort hospitalized for MI found that women are more likely than men to present with three or more associated symptoms (eg, epigastric symptoms; palpitations; and pain or discomfort in the jaw, neck, arms, or between the shoulder blades; 61.9% for women versus 54.8% for men). In adjusted analyses, women with an acute STEMI were more likely than men to present without chest pain (OR, 1.51). In comparison with men, women were more likely to perceive symptoms as stress/anxiety (20.9% versus 11.8%) but less likely to attribute symptoms to muscle pain (15.4% versus 21.2%).

One analysis found the following clinical features to be associated with acute MI: chest pain that radiates to the left, right, or both arms (LR, 2.3); diaphoresis (LR, 2.0); nausea and vomiting (LR, 1.9); third heart sound (LR, 3.2); systolic blood pressure less than or equal to 80 mm Hg (LR, 3.1); pulmonary crackles (LR, 2.1); any ST-segment

elevation greater than or equal to 1 mm (LR, 11.2); any ST depression (LR, 3.2); any Q wave (LR, 3.9); any conduction defect (LR, 2.7); and new conduction defect (LR, 6.3).

A meta-analysis reported the clinical features and risk factors with highest positive LRs for ACS were prior abnormal stress test (specificity, 96%; LR, 3.1), peripheral arterial disease (specificity, 97%; LR, 2.7), and pain radiation to both arms (specificity, 96%; LR, 2.6), as well as the following ECG findings: ST-segment depression (specificity, 95%; LR, 5.3) and any evidence of ischemia (specificity, 91%; LR, 3.6). Risk scores derived from both the HEART trial (https://www.mdcalc.com/heart-score-major-cardiac-events) and TIMI trial (https://www.mdcalc.com/timi-risk-score-ua-nstemi#use-cases) performed well in detecting ACS (LR, 13 for HEART score of 7-10, and LR, 6.8 for TIMI score of 5-7).

Hypertrophy of either ventricle or aortic stenosis may give rise to chest pain with less typical features. Pericarditis produces pain that may be greater when supine than upright and increases with breathing, coughing, or swallowing. Pleuritic chest pain is usually not ischemic, and pain on palpation may indicate a musculoskeletal cause.

Aortic dissection classically produces an abrupt onset of tearing pain of great intensity that often radiates to the back; however, this classic presentation occurs in a small proportion of cases. Anterior aortic dissection can also lead to myocardial or cerebrovascular ischemia.

In PE, chest pain is present in about 75% of cases. The chief objective in evaluating patients with suspected PE is to assess the clinical risk for VTE based on medical history and associated symptoms and signs (see above and

Chapter 9). Rupture of the thoracic esophagus iatrogenically or from vomiting is another cause of chest pain.

Findings on physical examination can occasionally yield important clues to the underlying cause of chest pain; however, a normal physical examination should never be used as the sole basis for ruling out most causes of chest pain, particularly ACS and aortic dissection. Vital signs (including pulse oximetry) and cardiopulmonary examination are the first steps for assessing the urgency and tempo of the subsequent examination and diagnostic workup. Although chest pain that is reproducible or worsened with palpation strongly suggests a musculoskeletal cause, up to 15% of patients with ACS will have reproducible chest wall tenderness. In one study, reproducible chest pain had a negative predictive value of 98%. A prominent xyphoid process painful to palpation may indicate xiphodynia. Slipping rib syndrome should be suspected if the chest pain is reproduced by the examiner pulling superiorly and anteriorly under the costal margin with their fingers. Pointing to the location of the pain with one finger has been shown to be highly correlated with nonischemic chest pain.

Aortic dissection can result in differential blood pressures between arms (greater than 20 mm Hg), pulse amplitude deficits, and new diastolic murmurs. Although hypertension is considered the rule in patients with aortic dissection, systolic blood pressure less than 100 mm Hg is present in up to 25% of patients.

A cardiac friction rub represents pericarditis until proven otherwise. It can best be heard with the patient sitting forward at end-expiration. Tamponade should be excluded in all patients with a clinical diagnosis of pericarditis by assess-

ing pulsus paradoxus (a decrease in systolic blood pressure greater than 10 mm Hg during inspiration) and inspection of jugular venous pulsations. Subcutaneous emphysema is common following cervical esophageal perforation but present in only about one-third of thoracic perforations (ie, those most commonly presenting with chest pain).

The absence of abnormal physical examination findings in patients with suspected PE usually serves to increase its likelihood, although a normal physical examination is also compatible with the more common conditions of panic/anxiety disorder and musculoskeletal disease.

1, ECG—Unless a competing diagnosis can be confirmed, an ECG is warranted in the initial evaluation of most patients with acute chest pain to help exclude ACS. When compared with White patients, Black patients who came to the emergency department with chest pain were less likely to have an ECG ordered (adjusted OR = 0.82). In a study of 11 emergency departments in Italy, 67% of patients with confirmed ACS had new-onset alterations of the ECG (compared with only 6.2% among non-ACS patients). ST-segment elevation is the ECG finding that is the strongest predictor of acute MI; however, up to 20% of patients with ACS can have a normal ECG.

In the emergency department, patients with suspected ACS can be safely removed from cardiac monitoring if they are pain-free at initial clinician assessment and have a normal or nonspecific ECG. This decision rule had 100% sensitivity for serious arrhythmia. Clinically stable patients with CVD risk factors, normal ECG, normal cardiac biomarkers, and no alternative diagnoses (such as typical GERD or costochondritis) should be followed up with a

timely exercise stress test that includes perfusion imaging. However, more than 25% of patients with stable chest pain referred for noninvasive testing will have normal coronary arteries and no long-term clinical events. The ECG can also provide evidence for alternative diagnoses, such as pericarditis and PE.

2. Troponins—Diagnostic protocols using a single high-sensitivity troponin assay combined with a standardized clinical assessment are an efficient strategy to rapidly determine whether patients with chest pain are at low risk and may be discharged from the emergency department. A study of the modified HEART score using a single blood draw of either high-sensitivity troponin (3.9 ng/L), high-sensitivity troponin I (0.9 ng/L), or conventional troponin I (0.0 ng/L) at presentation had a sensitivity of 100% for 30-day major adverse cardiac events.

Point-of-care troponin testing during ambulance transport to the emergency department has been found to have good specificity and positive predictive value (99.2% and 85.7%) but poor sensitivity (26.5%).

3. Risk scores—Six established risk scores for predicting acute MI are (1) the revised Goldman Risk Score, (2) TIMI Risk Score, (3) Global Registry of Acute Cardiac Events Risk Score, (4) HEART Risk Score, (5) Vancouver Chest Pain Rule, and (6) the European Society of Cardiology (ESC) 0/1, 0/2, 0/3-h algorithm. A study comparing these risk scores (not including the ESC algorithm) for predicting acute MI within 30 days reported a sensitivity of 98% (which correlates with a negative predictive value of greater than or equal to 99.5%). Patients eligible for discharge (about 30%) were those with a TIMI score of less than or

equal to 1, modified Goldman score of less than or equal to 1 with normal high-sensitivity troponin T, TIMI score of 0, or HEART score of less than or equal to 3 with normal high-sensitivity troponin I. In Black patients with average cardiovascular risk, HEART score is a better predictive tool for 6-week major adverse cardiac events when compared to TIMI score. Six-week major adverse cardiac events among patients with a low-risk HEART score (0-3) was 0.9-1.7%. However, the HEART score performs poorly in stratifying risk from cocaine-associated chest pain and does not eliminate the potential for gender bias. A study found that female patients with high HEART scores were admitted to the hospital from the emergency room at much lower rates than male patients with similar HEART scores.

4. Chest radiography—CXR is often useful in the evaluation of chest pain and is always indicated when cough or shortness of breath accompanies chest pain. Findings of pneumomediastinum or new pleural effusion are consistent with esophageal perforation.

5. Stress echocardiography—Stress echocardiography is useful in risk stratifying patients with chest pain, even among those with significant obesity. Patients who arrive at the emergency department with chest pain of intermediate or high probability for ACS without electrocardiographic or biomarker evidence of an MI can be safely discharged from an observation unit after stress cardiac MRI.

6. Coronary CT angiography—Sixty-four-slice coronary CT angiography is an alternative to stress testing in the emergency department for detecting ACS among patients with normal or nonspecific ECG and normal biomarkers. A meta-analysis of nine studies found CT angiography had

an estimated sensitivity of 95% for ACS and specificity of 87%, yielding a negative LR of 0.06 and a positive LR of 7.4. Functional testing appears to be the best initial noninvasive test in symptomatic patients with suspected CAD. CT angiography is an option for patients who do not have access to functional testing. CT-derived fractional flow reserve in acute chest pain has higher specificity for anatomic and physiologic assessment of coronary artery stenosis compared with coronary CT angiography.

A minimal-risk model developed by the PROMISE investigators includes 10 clinical variables that correlate with normal coronary CT angiography results and no clinical events, and thus safely managed without hospital admission and for whom noninvasive testing may be deferred: (1) younger age (mean 57.5); (2) female sex; (3) racial or ethnic minority; (4-6) no history of hypertension, diabetes, or dyslipidemia; (7) no family history of premature CAD; (8) never smoked cigarettes; (9) symptoms unrelated to physical or mental stress; and (10) higher HDL cholesterol level. In the PROMISE trial, women had higher rates of normal noninvasive testing compared with men, but women with abnormalities on such testing were less likely to be referred for catheterization or to receive statin therapy.

In the evaluation of PE, diagnostic test decisions and results must be interpreted in the context of the clinical likelihood of VTE. A negative D-dimer test is helpful for excluding PE in patients with low clinical probability of VTE (3-month incidence = 0.5%); however, the 3-month risk of VTE among patients with intermediate and high risk of VTE is sufficiently high in the setting of a negative

D-dimer test (3.5% and 21.4%, respectively) to warrant further imaging given the life-threatening nature of an untreated PE. CT angiography has replaced ventilation-perfusion scanning as the preferred initial diagnostic test, having approximately 90-95% sensitivity and 95% specificity for detecting PE (compared with pulmonary angiography). However, for patients with high clinical probability of VTE, lower extremity ultrasound or pulmonary angiogram may be indicated even with a normal helical CT.

Panic disorder is a common cause of chest pain, accounting for up to 25% of cases that present to emergency departments and a higher proportion of cases presenting in primary care office practices. Features that correlate with an increased likelihood of panic disorder include absence of CAD, atypical quality of chest pain, female sex, younger age, and a high level of self-reported anxiety. Depression is associated with recurrent chest pain with or without CAD (OR, 2.11).

Treatment of chest pain should be guided by the underlying etiology. The term “noncardiac chest pain’ is used when a diagnosis remains elusive after an extensive workup. Almost half of patients with noncardiac chest pain reported symptom improvement with high-dose PPI therapy. Relief of constipation may be therapeutic in PPI refractory noncardiac chest pain. A meta-analysis of 15 trials suggested modest to moderate benefit for psychological (especially cognitive-behavioral) interventions. It is unclear whether tricyclic or SSRI antidepressants have benefit in noncardiac chest pain. Hypnotherapy may offer some benefit.

¢ Refer patients with angina that is poorly controlled using maximal medical therapy to a cardiologist.

¢ Refer patients with poorly controlled, noncardiac chest pain to a pain specialist.

« Refer patients with sickle cell anemia to a hematologist.

« Failure to adequately exclude life-threatening causes of chest pain, particularly MI, dissecting aortic aneurysm, PE, and esophageal rupture.

¢ Patients with high-risk of complications from PE, or when PE is likely despite negative spiral CT.

« TIMI score of 1 or more, HEART score greater than 3, abnormal ECG, and abnormal 0- and 2-hour troponin tests.

« Pain control for rib fracture that impairs gas exchange.

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=== PALPITATIONS ===

> Forceful, rapid, or irregular beating of the heart.
> Rate, duration, and degree of regularity of heart-beat; age at first episode.
> Factors that precipitate or terminate episodes.
Light-headedness or syncope; neck pounding.
>» Chest pain; history of MI or structural heart disease.
Palpitations are defined as an unpleasant awareness of the forceful, rapid, or irregular beating of the heart. They are

the primary symptom for approximately 16% of patients presenting to an outpatient clinic with a cardiac complaint. Palpitations are experienced in 3.3% to 11.5% of pregnancies. In a study of palpitations at an outpatient cardiac unit, cardiac arrhythmias were the cause of palpitations in 81% of cases. Palpitations represent 5.8 of every 1000 emergency department visits, with an admission rate of 24.6%. While palpitations are usually benign, they are occasionally the symptom of a life-threatening arrhythmia. To avoid missing a dangerous cause of the patient's symptom, clinicians sometimes pursue costly and invasive testing when a conservative diagnostic evaluation is sufficient. The converse is also true. Table 2-3 lists history, physical examination, and ECG findings suggesting a cardiovascular cause for the palpitations.

When assessing a patient with palpitations in an acute care setting, the clinician must ascertain whether the symptoms represent (1) significant CVD, (2) a cardiac manifestation of a systemic disease such as thyrotoxicosis,

Table 2-3. Palpitations: Patients at high risk for a cardiovascular cause.

Historical risk factors

Family history of significant arrhythmias

Personal or family history of syncope or resuscitated from sudden death

History of MI

Palpitations that occur during sleep

Anatomic abnormalities

Structural heart disease such as dilated or hypertrophic cardiomyopathies

Valvular disease (stenotic or regurgitant)

EGG findings

Long QT syndrome

Bradycardia

Second- or third-degree heart block

Sustained ventricular arrhythmias

(3) an arrhythmia that is minor and transient, or (4) a benign somatic symptom that is amplified by the patient's underlying psychological state.

Etiology

Patients with palpitations who seek medical attention in an emergency department instead of a medical clinic are more likely to have a cardiac cause (47% versus 21%), whereas psychogenic causes are more common among those who seek attention in office practices (45% versus 27%). In a study of patients who went to a university medical clinic with the chief complaint of palpitations, causes were cardiac in 43%, psychogenic in 31%, and miscellaneous in 10%.

Cardiac arrhythmias that can result in symptoms of palpitations include sinus bradycardia; atrial fibrillation or flutter; sinus, supraventricular, and ventricular tachycardia; premature ventricular and atrial contractions; sick sinus syndrome; and advanced atrioventricular block. Structural cardiac conditions that lead to palpitations due to cardiac arrhythmias include valvular heart diseases, such as aortic regurgitation or stenosis, atrial or ventricular septal defect, cardiomyopathy, congenital heart disease, pericarditis, arrhythmogenic RV cardiomyopathy, and atrial myxoma. Mitral valve prolapse is not associated with arrhythmic events, but ventricular arrhythmias are frequent in mitral annulus disjunction.

Pericardial or myocardial infection with SARS-CoV-2, tuberculosis, and Trypanosoma cruzi (Chagas disease) can cause palpitations.

The most common psychogenic causes of palpitations are anxiety and panic disorder. The release of catecholamines during a significant stress or panic attack can trigger an arrhythmia. Asking a single question, “Have you experienced brief periods, for seconds or minutes, of an overwhelming panic or terror that was accompanied by racing heartbeats, shortness of breath, or dizziness?” can help identify patients with panic disorder.

Other causes of palpitations include fever, dehydration, hypoglycemia, anemia, thyrotoxicosis, mastocytosis, and pheochromocytoma. Drugs (such as cocaine, alcohol, caffeine, pseudoephedrine, cannabis, and illicit ephedra), prescription medications and drugs that prolong the QT interval (eg, digoxin, amitriptyline, erythromycin, methylphenidate), class 1 antiarrhythmics, dihydropyridine calcium channel blockers, acetylcholinesterase inhibitors, phenothiazines, theophylline, chemotherapeutic agents, and beta-agonists can precipitate palpitations.

Guiding the patient through a careful description of their palpitations may indicate a mechanism and narrow the differential diagnosis. Pertinent questions include the age at first episode; precipitants; and rate, duration, and degree of regularity of the heartbeat during the subjective palpitations. Palpitations lasting less than 5 minutes and a family history of panic disorder reduce the likelihood of an arrhythmic cause (LR+ = 0.38 and LR+ = 0.26, respectively). To better understand the symptom, ask patients to “tap out” the rhythm with their fingers. The circumstances

associated with onset and termination can also be helpful in determining the cause. Palpitations that start and stop abruptly suggest supraventricular or ventricular tachycardias. Termination of palpitations using vagal maneuvers (eg, Valsalva maneuver or forced coughing) suggests supraventricular tachycardia.

Three common descriptions of palpitations are (1) "flip-flopping" (or "stop and start"), often caused by premature contraction of the atrium or ventricle, with the perceived "stop" from the pause following the contraction, and the "start" from the subsequent forceful contraction; (2) rapid "fluttering in the chest," with regular "fluttering" suggesting supraventricular or ventricular arrhythmias (including sinus tachycardia) and irregular "fluttering" suggesting atrial fibrillation, atrial flutter, or tachycardia with variable block; and (3) "pounding in the neck" or neck pulsations, often due to "cannon" A waves in the jugular venous pulsations that occur when the right atrium contracts against a closed tricuspid valve (common with premature ventricular contractions and atrial ventricular dissociation).

Palpitations associated with chest pain suggest ischemic heart disease, or if the chest pain is relieved by leaning forward, pericardial disease. Palpitations associated with light-headedness, presyncope, or syncope suggest hypotension and may signify a life-threatening cardiac arrhythmia. Palpitations that occur regularly with exertion suggest silent ischemia, a rate-dependent bypass tract, or hypertrophic cardiomyopathy. If a benign etiology cannot be ascertained at the initial visit, ambulatory monitoring or prolonged inpatient cardiac monitoring

might be warranted.

Noncardiac symptoms should be elicited since palpitations may be caused by a normal heart responding to a metabolic or inflammatory condition. Weight loss suggests hyperthyroidism. Palpitations can be precipitated by vomiting or diarrhea causing electrolyte disorders and hypovolemia. Hyperventilation, hand tingling, and nervousness are common when anxiety or panic disorder is the cause of the palpitations. Palpitations associated with flushing, episodic hypertension, headaches, anxiety, and diaphoresis may be caused by a pheochromocytoma or paraganglioma. A family history of palpitations or sudden death suggests an inherited etiology such as long QT syndrome or Brugada syndrome. Chagas disease may cause palpitations and acute myocarditis. Younger patients should be asked about consumption of “energy drinks.” Dual use of cigarettes and e-cigarettes may cause palpitations.

Careful cardiovascular examination can find abnormalities that increase the likelihood of specific cardiac arrhythmias. The midsystolic click of mitral valve prolapse suggests the diagnosis of a supraventricular arrhythmia. The harsh holosystolic murmur of hypertrophic cardiomyopathy, which occurs along the left sternal border and increases with the Valsalva maneuver, suggests atrial fibrillation or ventricular tachycardia. A crescendo mid-diastolic murmur may be caused by an atrial myxoma. The presence of dilated cardiomyopathy, suggested by a displaced and enlarged cardiac point-of-maximal impulse, increases the likelihood of ventricular tachycardia and atrial fibrillation. In patients with chronic atrial fibrillation, in-office exercise (eg, a brisk walk in the hallway) may reveal an intermittent

accelerated ventricular response. The clinician should look for signs of hyperthyroidism (eg, tremulousness, brisk deep tendon reflexes, or fine hand tremor) or signs of stimulant drug use (eg, dilated pupils or skin or nasal septal perforations). Visible neck pulsations (LR+, 2.68) in association with palpitations increase the likelihood of atrioventricular nodal reentry tachycardia.

1. ECG—A 12-lead ECG should be performed on all patients reporting palpitations; although, in most instances, a specific arrhythmia will not be detected. Evidence of prior MI on ECG (eg, Q waves) increases the patient's risk of nonsustained or sustained ventricular tachycardia. Ventricular preexcitation (Wolff-Parkinson-White syndrome) is suggested by a short PR interval (less than 0.20 ms) and delta waves (upsloping PR segments). Left atrial enlargement (a terminal P-wave force in V1 more negative than 0.04 ms and notching in lead II) reflects an increased risk of atrial fibrillation. A prolonged QT interval and abnormal T-wave morphology suggest the long QT syndrome and an increased risk of ventricular tachycardia.

2. Monitoring devices—For high-risk patients (Table 2-3), further diagnostic studies are warranted. A stepwise approach has been suggested—starting with ambulatory monitoring devices (ambulatory ECG monitoring if the palpitations are expected to occur within the subsequent 72-hour period, event monitoring if less frequent). An implantable loop recorder can be used for extended monitoring if clinical suspicion is high and symptom to rhythm correlation cannot be otherwise established. Although the use of an implantable loop recorder has traditionally been reserved for patients experiencing syncope, the diagnostic

yield of this device may be cost-effective for a broader range of patients. In patients with recurrent unexplained palpitations, a single-lead, lightweight, continuously recording ambulatory adhesive patch monitor (Zio Patch) worn for 14-21 days increases diagnostic yield while reducing the cost of diagnosis. Inpatient continuous monitoring is indicated if serious arrhythmias are strongly suspected despite normal findings on the ambulatory monitoring; invasive electrophysiologic testing should be done if the ambulatory or inpatient monitor records a worrisome arrhythmia.

In patients with a prior MI, ambulatory cardiac monitoring or signal-averaged ECG is an appropriate next step to help exclude ventricular tachycardia. ECG exercise testing is appropriate in patients with suspected CAD and in patients who have palpitations with physical exertion. Echocardiography is useful when physical examination or ECG suggests structural abnormalities or decreased ventricular function.

After ambulatory monitoring, most patients with palpitations are found to have benign atrial or ventricular ectopy or nonsustained ventricular tachycardia. In patients with structurally normal hearts, these arrhythmias are not associated with adverse outcomes. Abstention from caffeine and tobacco may help. Often, reassurance suffices. If not, or in symptomatic patients, a trial of a beta-blocker may be prescribed. A three-session course of cognitive-behavioral therapy that includes some physical activity has proven effective for patients with benign palpitations with or without chest pain. For treatment of specific atrial or ventricular arrhythmias, see Chapter 12.

« For electrophysiologic studies.

¢ For advice regarding treatment of atrial or ventricular arrhythmias.

¢ Palpitations associated with syncope or near-syncope, particularly when the patient is aged 75 years or older and has an abnormal ECG, hematocrit less than 30%, shortness of breath, respiratory rate higher than 24/min, or a history of HE.

¢ Patients with risk factors for a serious arrhythmia.

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=== LOWER EXTREMITY EDEMA ===

History of VTE.

Symmetry of swelling.

Pain.

Change with dependence.

vvvvy

Hyperpigmentation, stasis dermatitis, lipodermatosclerosis, ulceration.

Acute and chronic lower extremity edema present important diagnostic and treatment challenges. Chronic venous insufficiency is by far the most common cause, affecting up to 2% of the population, and the incidence of venous insufficiency has not changed over the past 25 years. Venous insufficiency is a common complication of DVT; however, only a small number of patients with chronic venous insufficiency report a history of this disorder. Venous ulceration commonly affects patients with chronic venous insufficiency, and its management is labor-intensive and expensive. Normal lower extremity venous pressure (in the erect position: 80 mm Hg in deep veins, 20-30 mm Hg in superficial veins) and cephalad venous blood flow require competent bicuspid venous valves, effective muscle contractions, normal ankle range of motion, and normal respirations. When one or more of these components fail, venous hypertension may result. Chronic edema increases the risk of cellulitis with risk increasing as the stage of edema increases. Adults with unilateral or bilateral chronic edema have a 37-47% lifetime prevalence of cellulitis.

A. Symptoms and Signs

1. Unilateral lower extremity edema—Among common causes of unilateral lower extremity swelling, DVT is the most life-threatening. Clues suggesting DVT include a history of cancer, recent limb immobilization, or confinement to bed for at least 3 days following major surgery within the past month (Table 2-4). Adults with varicose veins have a significantly increased risk of DVT. Lower extremity swelling and inflammation in a limb recently affected by DVT

could represent anticoagulation failure and thrombus recurrence but more often are caused by postphlebitic syndrome with valvular incompetence. Other causes of a painful, swollen calf include cellulitis, musculoskeletal disorders (Baker cyst rupture [“pseudothrombophlebitis”]), gastrocnemius tear or rupture, calf strain or trauma, and left common iliac vein compression (May-Thurner syndrome), complex regional pain syndrome, diabetic myonecrosis, as well as other sites of nonthrombotic venous outflow obstruction, such as the inguinal ligament, iliac bifurcation, and popliteal fossa.

Table 2-4. Risk stratification of adults referred for ultrasound to rule out DVT.

Step 1:
Score 1 point for each
Untreated malignancy
Paralysis, paresis, or recent plaster immobilization
Recently bedridden for > 3 days due to major surgery within 4 weeks
Localized tenderness along distribution of deep venous system
Entire leg swelling
Swelling of one calf > 3 cm more than the other (measured 10 cm below tibial tuberosity)
Ipsilateral pitting edema
Collateral superficial (nonvaricose) veins
Previously documented DVT
Step 2:
Subtract 2 points if alternative diagnosis has equal or greater likelihood than DVT
Step 3:
Obtain sensitive D-dimer for score > 0

Score D-Dimer Positive’ D-Dimer Negative

0-1 Obtain ultrasound Ultrasound not required

22 Obtain ultrasound

''Positive"is above local laboratory threshold based on specific test and patient age.

2. Bilateral lower extremity edema—Bilateral involvement and significant improvement upon awakening favor systemic causes (eg, venous insufficiency) and can be presenting symptoms of volume overload (HE, cirrhosis, kidney disease [eg, nephrotic syndrome]). The most frequent symptom of chronic venous insufficiency is the sensation of “heavy legs,” followed by itching. Chronic exposure to elevated venous pressure accounts for the brawny, fibrotic skin changes observed in patients with chronic venous insufficiency as well as the predisposition toward skin ulceration, particularly in the medial malleolar area. Pain, particularly if severe, is uncommon in uncomplicated venous insufficiency.

Lower extremity swelling is a familiar complication of therapy with calcium channel blockers (particularly felodipine and amlodipine), pioglitazone, gabapentin, and minoxidil. Prolonged airline flights (longer than 10 hours) are associated with edema even in the absence of DVT.

Physical examination should include assessment of the heart, lungs, and abdomen for evidence of pulmonary hypertension (primary or secondary to chronic lung disease), HE, or cirrhosis. The skin findings related to chronic venous insufficiency depend on the severity and chronicity of the disease, ranging from hyperpigmentation and stasis dermatitis to abnormalities highly specific for chronic venous insufficiency: lipodermatosclerosis (thick, brawny

skin; in advanced cases, the lower leg resembles an inverted champagne bottle) and atrophie blanche (small, depigmented macules within areas of heavy pigmentation). The size of both calves should be measured 10 cm below the tibial tuberosity and pitting and tenderness elicited. Swelling of the entire leg or of one leg 3 cm more than the other suggests deep venous obstruction. The left calf is normally slightly larger than the right as a result of the left common iliac vein coursing under the aorta.

A shallow, large, modestly painful ulcer located over the medial malleolus is a hallmark of chronic venous insufficiency, whereas small, deep, and more painful ulcers over the lateral malleolus are more apt to be due to arterial insufficiency, vasculitis, or infection. Diabetic vascular ulcers, however, may be painless. When an ulcer is on the foot or above the mid-calf, causes other than venous insufficiency should be considered.

The physical examination is usually inadequate to distinguish lymphedema from venous insufficiency. Only the Kaposi-Stemmer sign (the inability to pinch or pick up a fold of skin at the base of the second toe because of its thickness) is a significant predictor of lymphedema (OR,

=== 7.9; P = 0.02). ===

Patients without an obvious cause of acute unilateral lower extremity swelling (eg, calf strain) should have an ultrasound performed, since DVT is difficult to exclude on clinical grounds. A prediction rule allows a clinician to exclude a lower extremity DVT in patients without an ultrasound if

the patient has low pretest probability for DVT and a negative sensitive D-dimer test (the “Wells prediction rule”) (https://www.mdcalc.com/wells-criteria-pulmonary-embolism) (Chapter 9).

The diagnostic study of choice to detect chronic venous insufficiency due to venous incompetence is duplex ultrasonography. Assessment of the ankle-brachial pressure index is important in the management of chronic venous insufficiency since peripheral arterial disease may be exacerbated by compression therapy. Caution is required in interpreting the results of ankle-brachial pressure index in older patients and diabetic patients due to the decreased compressibility of their arteries. A urine dipstick test that is strongly positive for protein can suggest nephrotic syndrome, and a serum creatinine can estimate kidney function. Measuring serum albumin can further assess for nephrotic syndrome or chronic liver disease. Lymphoscintigraphy can be used to confirm a clinical suspicion of lymphedema.

See relevant chapters for treatment of edema in patients (Chapter 18), and lymphedema and venous stasis ulcers (Chapter 14). Edema resulting from calcium channel blocker therapy responds to concomitant therapy with ACE inhibitors or ARBs.

In patients with chronic venous insufficiency without comorbid volume overload (eg, HF), it is best to avoid diuretic therapy. These patients have relatively decreased intravascular volume, and administration of diuretics may first enhance sodium retention through increased secretion of renin and angiotensin and then result in AKI and oliguria. Instead, the most effective treatment involves (1) leg elevation, above the level of the heart, for

30 minutes three to four times daily, and during sleep; (2) compression therapy; and (3) ambulatory exercise to increase venous return through calf muscle contractions.

A wide variety of stockings and devices are effective in decreasing swelling and preventing ulcer formation and reducing the risk of cellulitis. They should be put on with awakening before hydrostatic forces result in edema. To control mild edema, 20-30 mm Hg compression is usually sufficient, whereas 30-40 mm Hg compression is usually required to control moderate to severe edema associated with ulcer formation. To maintain improvement, consider switching from an elastic stocking to one made of inelastic grosgrain material. Patients with decreased ankle-brachial pressure index should be managed in concert with a vascular surgeon. Compression stockings (12-18 mm Hg at the ankle) are effective in preventing edema and asymptomatic thrombosis associated with long airline flights in low- to medium-risk persons, and compression therapy decreases recurrence of cellulitis among patients with chronic venous insufficiency. Support stockings are recommended for pregnant women during air travel. For lymphedema, bandaging systems applied twice weekly can be effective. Multi-component compression bandaging may offer additional benefit. Short-term manual lymphatic drainage treatment may improve chronic venous insufficiency severity, symptoms, and quality of life. For patients with reduced mobility and leg edema, intermittent pneumatic compression treatment can reduce edema and improve ankle range of motion.

Liposuction, suction-assisted lipectomy, and subcutaneous drainage may have treatment benefit if conservative

measures fail in treatment of lymphedema.

¢ Refer patients with chronic lower extremity ulcerations to wound care specialist.

« Refer patients with nephrotic syndrome to a nephrologist.

¢ Refer patients with coexisting severe arterial insufficiency (claudication) that would complicate treatment with compression stockings to a vascular surgeon.

« Pending definitive diagnosis in patients at high risk for DVT despite normal lower extremity ultrasound.

* Severe, acute swelling raising concern for an impending compartment syndrome.

« Severe edema that impairs ability to ambulate or perform activities of daily living.

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=== FEVER & HYPERTHERMIA ===

> Age; injection substance use.

Localizing symptoms; weight loss; joint pain.

> Immunosuppression or neutropenia; history of cancer, risk of COVID-19.

> Medications.

> Travel.

The average normal oral body temperature taken in mid-morning is 36.7°C (range 36-37.4°C). This range includes a mean and two standard deviations, thus encompassing 95% of a normal population (normal diurnal temperature variation is 0.5-1°C).

The normal rectal or vaginal temperature is 0.5°C higher than the oral temperature, and the axillary temperature is 0.5°C lower. However, a normal body temperature based on a peripheral thermometer (tympanic membrane, temporal artery, axillary, oral) does not always exclude the presence of a fever. To exclude a fever, a rectal temperature is more reliable than an oral temperature (particularly in patients who breathe through their mouth, who are tachypneic, or who are in an ICU setting where a rectal temperature probe can be placed to detect fever).

Fever is a regulated rise to a new “set point” of body temperature in the hypothalamus induced by pyrogenic cytokines. These cytokines include IL-1, TNF, interferon-gamma, and IL-6. The elevation in temperature results from either increased heat production (eg, shivering) or decreased heat loss (eg, peripheral vasoconstriction). Hyperthermia—not mediated by cytokines—occurs when body metabolic heat production (as in thyroid storm) or environmental heat load exceeds normal heat loss capacity or when there is impaired heat loss (eg, heat stroke). Body temperature in cytokine-induced fever seldom exceeds 41.1°C unless there is structural damage to hypothalamic regulatory centers; body temperature in hyperthermia may rise to levels (more than 41.1°C) capable of producing irreversible protein denaturation and resultant brain damage;

no diurnal variation is observed.

)> Clinical Findings

A. Fever

Fever as a symptom provides important information about the presence of illness—particularly infections—and about changes in the clinical status of the patient. Fever may be more predictive of bacteremia in elderly patients. The fever pattern, however, is of marginal value for most specific diagnoses except for the relapsing fever of malaria, borreliosis, and occasional cases of lymphoma, especially Hodgkin disease. Furthermore, the degree of temperature elevation does not necessarily correspond to the severity of the illness. Fever with rash and eosinophilia defines the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

In general, the febrile response tends to be greater in children than in adults. In older persons, neonates, and persons receiving certain medications (eg, NSAIDs, corticosteroids), rather than a fever, a normal temperature or even hypothermia may be observed. Markedly elevated body temperature may result in profound metabolic disturbances. Febrile patients admitted to a hospital with a body temperature above 39.5°C had higher mortality and AKI events compared to patients with less fever (38.0-38.1°C). High temperature during the first trimester of pregnancy may cause birth defects, such as anencephaly. Fever increases insulin requirements and alters the metabolism and disposition of drugs used for the treatment of the diverse diseases associated with fever.

The source of fever varies by population and setting. In a study of 92 patients who underwent shoulder arthroplasty

and developed fever, an infectious cause was found in only 6 patients. In the neurologic ICU, fever can occur directly from brain injury (called “central fever”). One model predicted “central fever” with 90% probability if a patient met all of the following criteria: (1) less than 72 hours of neurologic ICU admission; (2) presence of subarachnoid hemorrhage, intraventricular hemorrhage, or brain tumor; (3) absence of infiltrate on CXR; and (4) negative cultures. For patients in the ICU, elevated procalcitonin and CRP levels favor infection, rather than central fever, as the cause of fever.

Procalcitonin measurement at emergency department admission for patients with fever and a qSOFA (quick Sequential Organ Failure Assessment) (https://qsofa.org/#calc) less than 2 was not associated with better emergency department outcomes with the exception of a slight benefit with bloodstream infections. For patients with a qSOFA of 2 or higher, overall mortality was lower if they had procalcitonin-guided management in the emergency department (20.5% versus 26.5%).

Fever may also be more common in patients with other forms of trauma. In a study of 268 patients, including patients with multiple injuries (n = 59), isolated head injuries (n = 97), isolated body injuries (n = 100), and minor trauma (n = 12), the incidence of fever was similar in all groups irrespective of injury (11-24%). In all groups, there was a significant association between the presence of early fever and death in the hospital (6-18% versus 0-3%), as well as longer median ICU stays (3-7 days versus 2-3 days).

Spinal cord injury may cause fever by the loss of supraspinal control of the sympathetic nervous system and defective thermoregulation due to loss of sensation.

Among pregnant women, the prevalence of intrapartum fever of 38°C or greater in pregnancies of 36 weeks' gestation or more is 6.8% (1 in 15 women in labor), but the neonatal sepsis rate among affected mothers is 0.24% (less than 1 in 400 babies). This finding calls into question the need for universal laboratory work, cultures, and antibiotic treatment pending culture results for this newborn population.

Contrary to classical teaching, postoperative atelectasis probably does not cause fever. Febrile nonhemolytic transfusion reaction is common, occurring in about 1% of transfusion episodes, and is mediated by proinflammatory cytokines elaborated by donor leukocytes during storage.

B. Hyperthermia

Malignant catatonia is a disorder consisting of catatonic symptoms, hyperthermia, autonomic instability, and altered mental status.

Neuroleptic malignant syndrome, a variant of malignant catatonia, is a rare and potentially lethal idiosyncratic reaction to neuroleptic medications, particularly haloperidol and fluphenazine. It has also been reported with the atypical neuroleptics (such as olanzapine or risperidone) leptic malignant syndrome but occurs within hours of ingestion of agents that increase levels of serotonin in the CNS, including SSRIs, MAOIs, tricyclic antidepressants, meperidine, dextromethorphan, bromocriptine, tramadol, lithium, and psychostimulants (such as cocaine, methamphetamine, and MDMA) (see Chapter 40).

Clonus and hyperreflexia are more common in serotonin syndrome, whereas "lead pipe" rigidity is more common in neuroleptic malignant syndrome. Neuroleptic

malignant and serotonin syndromes share common clinical and pathophysiologic features with malignant hyperthermia of anesthesia (see Chapter 40).

C. Fever of Undetermined Origin

See Fever of Unknown Origin, Chapter 32.

Most fever is well tolerated. When the temperature is less than 40°C, symptomatic treatment only is required. The treatment of fever with antipyretics does not appear to affect mortality of critically ill patients or affect the number of ICU-free days. A temperature greater than 41°C is likely to be hyperthermia rather than cytokine-mediated fever, and emergent management is indicated. (See Heat Stroke, Chapter 39.)

A. General Measures for Removal of Heat

Regardless of the cause of the fever, alcohol sponges, cold sponges, ice bags, ice-water enemas, and ice baths will lower body temperature (see Chapter 39). They are more useful in hyperthermia since patients with cytokine-related fever will attempt to override these therapies.

B. Pharmacologic Treatment of Fever

1. Antipyretic drugs—Antipyretic therapy is only needed for patients with marginal hemodynamic status. It can, however, be used for symptomatic relief. Aspirin or acetaminophen, 325-650 mg orally every 4 hours, is effective in reducing fever. Early administration of acetaminophen to treat fever due to probable infection does not affect the number of ICU-free days. These drugs are best administered around the clock, rather than as needed, since “as needed” dosing results in periodic chills and sweats due to fluctuations in temperature caused by varying levels of drug.

2. Prophylactic antimicrobial therapy—Antibacterial and antifungal prophylactic regimens are recommended only for patients expected to have less than 100 neutrophils/mcL for more than 7 days, unless other factors increase risks for complications or mortality.

3. Empiric antimicrobial therapy—Empiric antibiotic therapy is sometimes warranted. Even before infection can be documented, prompt broad-spectrum antimicrobials are indicated for febrile patients who have hemodynamic instability, severe neutropenia (neutrophils less than 500/mcL [0.5 x 10°/L]), asplenia (surgical or from sickle cell disease), or immunosuppression (from HIV infection [see Chapter 33] or from medications such as systemic corticosteroids, azathioprine, cyclosporine) (Tables 32-1 and 32-5). Febrile neutropenic patients should receive initial doses of empiric antibacterial therapy within an hour of triage and should either be monitored for at least 4 hours to determine suitability for outpatient management or be admitted to the hospital (see Infections in the Immunocompromised Patient, Chapter 32). It is standard to admit patients to the hospital with febrile neutropenic episodes, although carefully selected patients may be managed as outpatients after systematic assessment beginning with a validated risk index (eg, Multinational Association for Supportive Care in Cancer [MASCC] score or Talcott rules). In the MASCC index calculation, low-risk factors include the following: age under 60 years (2 points), burden of illness (5 points for no or mild symptoms and 3 points for moderate symptoms), outpatient status (3 points), solid tumor or hematologic malignancy with no previous fungal

infection (4 points), no COPD (4 points), no dehydration requiring parenteral fluids (3 points), and systolic blood pressure greater than 90 mm Hg (5 points). Patients with MASCC scores of 21 or higher or in Talcott group 4 (presentation as an outpatient without significant comorbidity or uncontrolled cancer), and without other risk factors, can be managed safely as outpatients.

The carefully selected outpatients determined to be at low risk by MASCC score (particularly in combination with a normal serum CRP level) or by Talcott rules can be managed with an oral fluoroquinolone plus amoxicillin/clavulanate (or clindamycin, if penicillin allergic), unless fluoroquinolone prophylaxis was used before fever developed. For treatment of fever during neutropenia following chemotherapy, outpatient parenteral antimicrobial therapy can be provided effectively and safely in low-risk patients with a single agent such as cefepime, piperacillin/tazobactam, imipenem, meropenem, or doripenem.

High-risk patients should be referred for inpatient management with combination parenteral antimicrobial therapy based on specific risk factors such as pneumonia-causing pathogens or central line-associated bloodstream infections (see Infections in the Immunocompromised Patient and Table 32-1 in Chapter 32 and see Infections in Chapter 41).

If a fungal infection is suspected in patients with prolonged fever and neutropenia, fluconazole is an equally effective but less toxic alternative to amphotericin B.

C. Treatment of Hyperthermia

Discontinuation of the offending agent is mandatory.

Treatment of neuroleptic malignant syndrome includes

dantrolene in combination with bromocriptine or levodopa includes a central serotonin receptor antagonist—cyproheptadine or chlorpromazine—alone or in combination with a benzodiazepine (see Chapter 40). In patients for whom it is difficult to distinguish which syndrome is present, treatment with a benzodiazepine may be the safest therapeutic option.

« Presence of vital sign abnormalities or evidence of end-organ dysfunction in clinical cases when early sepsis is suspected.

« Febrile neutropenic patients at high risk for clinical decompensation.

+ For measures to control a temperature higher than 41°C or when fever is associated with seizure or other mental status changes.

« Heat stroke (see Chapter 39).

* Malignant catatonia; neuroleptic malignant syndrome; serotonin syndrome; malignant hyperthermia of anesthesia.

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=== INVOLUNTARY WEIGHT LOSS ===

>» Age; caloric intake; secondary confirmation (eg, changes in clothing size).
>» Fever; change in bowel habits.
> Substance use.
» Age-appropriate cancer screening history.
Body weight is determined by a person's caloric intake, absorptive capacity, metabolic rate, and energy losses. Body weight normally peaks by the fifth or sixth decade and then gradually declines at a rate of 1-2 kg per decade. In NHANES II, a national survey of community-dwelling older adults (aged 50-80 years), recent involuntary weight

loss (more than 5% usual body weight) was reported by 7% of respondents, and this was associated with a 24% higher mortality. In postmenopausal women, unintentional weight loss was associated with increased rates of hip and vertebral fractures.

> Etiology

Involuntary weight loss is regarded as clinically significant when it exceeds 5% or more of usual body weight over a 6- to 12-month period. It often indicates serious physical or psychological illness, but nonmalignant diseases more commonly cause unintentional weight loss than malignant causes. Physical causes are usually evident during the initial evaluation, but an easily identifiable cause is not found in 6-28% of cases. The most common causes are cancer (about 30%), GI disorders (about 15%), and dementia or depression (about 15%). At a university hospital in Thailand, the three most common causes of unintentional weight loss were reduced appetite (20.1%), dementia (13.7%), and medications (11.0%). Nearly half of patients with Parkinson disease have weight loss associated with disease progression. When an adequately nourished—-appearing patient complains of weight loss, inquiry should be made about exact weight changes (with approximate dates) and about changes in clothing size. Family members can provide confirmation of weight loss, as can old documents such as photographs from driver's licenses. A mild, gradual weight loss occurs in some older individuals because of decreased energy requirements. However, rapid involuntary weight loss is predictive of morbidity and mortality.

In addition to various disease states, causes in older individuals include loss of teeth and consequent difficulty with chewing, medications interfering with taste or causing nausea, alcohol use disorder, and social isolation. Among Black persons at an adult day health center, 65% had a significant nutritional disorder: 48.5% reported involuntary weight loss or gain, 21% ate fewer than two meals daily, and 41.2% had tooth loss or mouth pain.

Once the weight loss is established, the history, medication profile, physical examination, and conventional laboratory and radiologic investigations (eg, CBC, liver biochemical tests, kidney panel, serologic tests including HIV, TSH level, UA, fecal occult blood test, and CXR) usually reveal the cause. Age-appropriate cancer screening should be completed as recommended by guidelines (eg, Papanicolaou smear, mammography, fecal occult blood test/screening colonoscopy/flexible sigmoidoscopy, possibly PSA) (Chapter 1). Whole-body CT imaging is increasingly used for diagnosis; one study found its diagnostic yield to be 33.5%. Another study found a low yield from CT scanning with contrast of the abdomen and pelvis for the presence of malignancy (2.3%) in patients whose only symptom was weight loss.

When these tests are normal, the second phase of evaluation should focus on more definitive GI investigation (eg, tests for malabsorption, endoscopy). However, one prospective case study in patients with unintentional weight loss showed that colonoscopy did not find colorectal cancer if weight loss was the sole indication for the test.

If the initial evaluation is unrevealing, follow-up is pref-

erable to further diagnostic testing. Death at 2-year follow-up was not nearly as common in patients with unexplained involuntary weight loss (8%) as in those with weight loss due to malignant (79%) and established nonmalignant diseases (19%). Psychiatric consultation should be considered when there is evidence of depression, dementia, anorexia nervosa, or other emotional problems. Ultimately, in approximately 15-25% of cases, no cause for the weight loss can be found.

Malignancy, GI disorders (poorly fitting dentures, cavities, swallowing or malabsorption disorders, pancreatic insufficiency), HE, HIV, tuberculosis, psychological problems (dementia, depression, paranoia), endocrine disorders (hyper-, hypothyroidism, hyperparathyroidism, hypoadrenalism), Whipple disease, eating problems (dietary restrictions, lack of money for food, teeth problems), social problems (alcohol use disorder, social isolation), and medication side effects are all established causes.

Weight stabilization occurs in most surviving patients with both established and unknown causes of weight loss through treatment of the underlying disorder and caloric supplementation. Nutrient intake goals are established in relation to the severity of weight loss, in general ranging from 30-40 kcal/kg/day. In order of preference, route of administration options include oral, temporary nasojejunal tube, or percutaneous gastric or jejunal tube. Parenteral nutrition is reserved for patients with serious associated problems.

A variety of pharmacologic agents have been proposed for the treatment of weight loss. These can be categorized into appetite stimulants (corticosteroids, progestational agents, cannabinoids, and serotonin antagonists); anabolic agents

(growth hormone, ghrelin, and testosterone derivatives); and anticatabolic agents (omega-3 fatty acids, pentoxifylline, hydrazine sulfate, and thalidomide). There is no evidence that appetite stimulants decrease mortality, and they may have severe adverse side effects. The anabolic agent nandrolone decanoate reversed weight and lean tissue loss in women with HIV, and human growth hormone temporarily increased weight and walking speed in undernourished elderly people. However, studies have not consistently shown mortality benefit.

Exercise training may prevent or even reverse the process of muscle wasting in HF ("cardiac cachexia'). Protein or creatine supplementation combined with resistance exercise training and aerobic activity may prevent aging-related attenuation of muscle mass and functional performance. Some patients with cancer-associated weight loss may benefit from nutritional assessment and intervention as decreased food intake may be playing a role. The effectiveness, acceptability, and safety of exercise training for adults with cancer cachexia has not been established.

« Weight loss caused by malabsorption.

¢ Persistent nutritional deficiencies despite adequate supplementation.

« Weight loss as a result of anorexia or bulimia.

« Severe protein-energy malnutrition, including the syndromes of kwashiorkor and marasmus.

« Vitamin deficiency syndromes.

* Cachexia with anticipated progressive weight loss secondary to unmanageable psychiatric disease.

¢ Careful electrolyte and fluid replacement in protein-energy malnutrition and avoidance of "re-feeding

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=== FATIGUE & SYSTEMIC INTOLERANCE DISEASE ===

(Chronic Fatigue Syndrome)
> Weight loss; fever.
>» Sleep-disordered breathing.
>» Medications; substance use.
Fatigue, as an isolated symptom, accounts for 1-3% of visits to generalists. The symptom of fatigue is often poorly described and less well defined by patients than symptoms associated with specific dysfunction of organ systems.
Fatigue or lassitude and the closely related complaints of

weakness, tiredness, and lethargy are often attributed to overexertion, poor physical conditioning, sleep disturbance, obesity, undernutrition, and emotional problems. A history of the patient's daily living and working habits may obviate the need for extensive and unproductive diagnostic studies.

Fatigue in older adults increases the risk of developing negative health outcomes (mortality OR, 2.14), the development of disabilities in basic activities of daily living (OR, 3.22), or the occurrence of physical decline (OR, 1.42).

A working case definition of chronic fatigue syndrome indicates that it is not a homogeneous abnormality, there is no single pathogenic mechanism and no physical finding or laboratory test can be used to confirm the diagnosis. The Institute of Medicine (now called the National Academy of Medicine) has recommended using the term systemic exertion intolerance disease (SEID). Other conditions identified as causing chronic fatigue include myalgic encephalitis and neurasthenia, each with specific diagnostic criteria creating inconsistent diagnoses and treatment plans.

A. Fatigue

Clinically relevant fatigue is composed of three major components: generalized weakness (difficulty in initiating activities); easy fatigability (difficulty in completing activities); and mental fatigue (difficulty with concentration and memory). Important diseases that can cause fatigue include hyper- and hypothyroidism, hyperparathyroidism, HF, infections (endocarditis, hepatitis), COPD, asthma, interstitial lung disease, ESKD, sleep apnea, anemia, autoimmune disorders, multiple sclerosis, IBS, Parkinson disease, cere-

bral vascular accident, and cancer. Solution-focused therapy has a significant initial beneficial effect on the severity of fatigue and quality of life in patients with quiescent IBD.

Alcohol use disorder, vitamin C deficiency (scurvy), side effects from medications (eg, sedatives and beta-blockers), and psychological conditions (eg, insomnia, depression, anxiety, panic attacks, dysthymia, and somatic symptom disorder may be the cause. Common outpatient infectious causes include mononucleosis and sinusitis. These conditions are usually associated with other characteristic signs, but patients may emphasize fatigue and not discuss their other symptoms unless directly asked. The lifetime prevalence of significant fatigue (present for at least 2 weeks) is about 25%. Fatigue of unknown cause or related to psychiatric illness exceeds that due to physical illness, injury, alcohol, or medications.

Although frequently associated with Lyme disease, severe fatigue as a long-term sequela is rare. Post traumatic brain injury fatigue and sleep disturbance may respond to a light box and in-home dynamic light therapy.

B. Systemic Exertion Intolerance Disease

Diagnosis of SEID requires the presence of all three of the following symptoms:

1. Substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.

2. Postexertional malaise.

3. Unrefreshing sleep.

In addition, the patient must have at least one of the following two manifestations: (1) cognitive impairment or (2) orthostatic intolerance (lightheadedness, dizziness, and headache that worsen with upright posture and improve with recumbency).

The evaluation of SEID includes a history and physical examination as well as CBC; ESR; kidney function; serum electrolytes, glucose, creatinine, calcium; liver biochemical tests and thyroid function tests; UA; tuberculin skin test; and screening questionnaires for psychiatric disorders. Other tests to be performed as clinically indicated are serum cortisol, ANA, rheumatoid factor, immunoglobulin levels, Lyme serology in endemic areas (although rarely a long-term complication of this infection), and HIV antibody. More extensive testing is usually unhelpful, including antibody to Epstein-Barr virus. There may be an abnormally high rate of postural hypotension.

Resistance training and aerobic exercise lessens fatigue and improves performance for a number of chronic conditions associated with a high prevalence of fatigue, including HF, COPD, arthritis, and cancer. Continuous positive airway pressure is an effective treatment for obstructive sleep apnea. Pitolisant, a selective histamine H,-receptor antagonist with wake-promoting effect, may reduce daytime sleepiness in patients with moderate to severe obstructive sleep apnea who decline continuous positive airway pressure treatment.

Psychostimulants such as methylphenidate have shown inconsistent results in randomized trials of treatment of cancer-related fatigue. Methylphenidate and cognitive-

behavioral therapy may improve mental fatigue and cognitive function in patients with traumatic brain injury. Modafinil and armodafinil appear to be effective, well-tolerated agents in patients who have HIV with fatigue and as adjunctive agents in patients who have depression or bipolar disorder with fatigue. Testosterone replacement in hypoandrogenic men over age 65 had no significant benefits for walking distance or vitality, as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue scale. However, men receiving testosterone reported slightly better mood and lower severity of depressive symptoms than those receiving placebo. Vitamin D treatment significantly improved fatigue in kidney transplantation patients as well as in otherwise healthy persons with vitamin D deficiency. Internet-based cognitive-behavioral therapy is effective in reducing severe fatigue in breast cancer survivors. Therapeutic Care (a complementary medicine modality that uses acupressure) reduces fatigue in some patients with breast cancer receiving chemotherapy, while moderate-intensity exercise did not. Six weeks of Swedish massage therapy reduced fatigue in female breast cancer survivors who had surgery plus radiation and/or chemotherapy/chemoprevention. There is limited and preliminary evidence that rasagiline, modafinil, and doxepin are associated with improvement of fatigue in Parkinson disease. Amantadine, modafinil, and methylphenidate were not found to be superior to placebo in improving fatigue associated with multiple sclerosis and caused more frequent adverse events.

The treatment of subclinical hypothyroidism is unlikely to benefit symptoms of fatigue. Oral melatonin

does not improve fatigue in patients with advanced cancer. Exceeding the RDA for protein intake does not increase muscle or physical function, nor augment anabolic response to testosterone in older men, nor reduce muscle soreness or fatigue after prolonged moderate-intensity walking exercise.

A variety of agents and modalities have been tried for the treatment of SEID without improvement in symptoms. Some patients with postural hypotension report response to increases in dietary sodium as well as fludrocortisone, 0.1 mg orally daily. The immunomodulator rintatolimod improved some measures of exercise performance compared with placebo in two trials (with low strength of evidence). Low-dose naltrexone is being used off-label with anecdotal reports of benefit. There is limited evidence that dietary modification is beneficial.

Patients with SEID have benefited from a comprehensive multidisciplinary intervention, including optimal medical management, treating any ongoing affective or anxiety disorder pharmacologically, and implementing a comprehensive cognitive-behavioral treatment program. At present, cognitive-behavioral therapy and graded exercise are the treatments of choice for patients with SEID.

> When to Refer

« Infections not responsive to standard treatment.

« Difficult-to-control hyper- or hypothyroidism.

« Severe psychological illness.

¢ Malignancy.

¢ Failure to thrive.

« Fatigue severe enough to impair activities of daily living.

Bateman L et al. Myalgic encephalomyelitis/chronic fatigue syndrome: essentials of diagnosis and management. Mayo Clin Proc. 2021;96:2861. [PMID: 34454716]
Chapman EJ et al. Practice review: evidence-based and effective management of fatigue in patients with advanced cancer. Palliat Med. 2022;36:7. [PMID: 34903113]
Knoop V et al; Gerontopole Brussels Study group. Fatigue and the prediction of negative health outcomes: a systematic review with meta-analysis. Ageing Res Rev. 2021;67:101261.

=== [PMID: 33548508] ===

Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2021 Oct 29.

=== [PMID: 35438859] ===

=== ACUTE HEADACHE ===

> Age > 40 years.
> Rapid onset and severe intensity (ie, “thunderclap” headache), trauma, onset during exertion.
> Fever, vision changes, neck stiffness.
> HIV infection.
> Current or past history of hypertension.
> Neurologic findings (mental status changes,

motor or sensory deficits, loss of consciousness).

Approximately 90% of people in the United States experience a headache in their lifetime. A broad range of disorders only with acute nontraumatic headache in adults and adolescents. The challenge in the initial evaluation of acute headache is to identify which patients are presenting with an uncommon but life-threatening condition; approximately 1% of patients seeking care in emergency department settings and considerably less in office practice settings fall into this category.

Diminution of headache in response to typical migraine therapies (such as serotonin receptor antagonists or ketorolac) does not rule out critical conditions such as subarachnoid hemorrhage or meningitis as the underlying cause.

A “sentinel headache” before a subarachnoid hemorrhage is a sudden, intense, persistent headache different from previous headaches; it precedes subarachnoid hemorrhage by days or weeks and occurs in 15-60% of patients with spontaneous subarachnoid hemorrhage.

A careful history and physical examination should aim to identify causes of acute headache that require immediate treatment. These causes can be broadly classified as (1) imminent or completed vascular events (intracranial hemorrhage, thrombosis, cavernous sinus thrombosis, vasculitis, malignant hypertension, arterial dissection, cerebral venous thrombosis, transient ischemic attack, or aneurysm); (2) infections (abscess, encephalitis, or meningitis), intracranial masses causing intracranial hypertension, preeclampsia; and (3) carbon monoxide poisoning and methemoglobinemia. Having the patient carefully describe the onset of headache can help diagnose a serious cause.

Report of a sudden-onset headache that reaches maximal and severe intensity within seconds or a few minutes is the classic description of a “thunderclap” headache; it should precipitate workup for subarachnoid hemorrhage, since the estimated prevalence of subarachnoid hemorrhage in patients with thunderclap headache is 43%. Thunderclap headache during the postpartum period precipitated by the Valsalva maneuver or recumbent positioning may indicate reversible cerebral vasoconstriction syndrome or irreversible cerebral venous sinus thrombosis. Venous-specific imaging sequences may be needed for diagnosis. Other historical features that raise the need for diagnostic testing include headache brought on by cough, exertion, or sexual activity.

The medical history can guide the need for additional workup. Under most circumstances (including a normal neurologic examination), new headache in a patient older than 50 years or with HIV infection warrants immediate neuroimaging (Table 2-5). When the patient has a history of hypertension—particularly uncontrolled hypertension—a complete search for other features of “malignant hypertension” is appropriate to determine the urgency of control of hypertension (see Chapter 13). Headache and hypertension associated with pregnancy may be due to preeclampsia. Episodic headache associated with the triad of hypertension, palpitations, and sweats is suggestive of pheochromocytoma. In the absence of thunderclap headache, advanced age, and HIV infection, a careful physical examination and detailed neurologic examination will usually determine acuity of the workup and need for further diagnostic testing. A history consistent with hypercoagulability is associ-

ated with an increased risk of cerebral venous thrombosis.

Symptoms can be useful for diagnosing migraine headache in the absence of the “classic” migraine pattern of scintillating scotoma followed by unilateral headache, photophobia, and nausea and vomiting (Table 2-6). The presence of three or more of these symptoms (nausea, photophobia, phonophobia, and exacerbation by physical activity) can establish the diagnosis of migraine

Table 2-5. Clinical features associated with acute headache that warrant urgent or emergent neuroimaging.

Indications for neuroimaging prior to lumbar puncture
Abnormal neurologic examination (particularly focal neurologic deficits)
Abnormal mental status
Abnormal funduscopic examination (papilledema; loss of venous pulsations)
Meningeal signs
Indications for emergent neuroimaging completed prior to leaving office or emergency department
Abnormal neurologic examination
“Thunderclap” headache
Patients with HIV with new type of headache!
Indications for urgent neuroimaging scheduled prior to leaving office or emergency department
Age > 50 years (normal neurologic examination) with new type of headache
‘Use CT with or without contrast or MRI if HIV positive.

Data from American College of Emergency Physicians. Clinical policy: critical issues in the evaluation and management of patients presenting to the emergency department with acute

headache. Ann Emerg Med. 2008;52:407.

(in the absence of other clinical features that warrant neuroimaging studies), and the presence of only one or two symptoms (provided one is not nausea) can help rule out migraine. A systematic list called the SNNOOP10 has been developed as a screening method for secondary causes of headache (Table 2-7).

Critical components of the physical examination of a patient with acute headache include vital signs, neurologic examination, and vision testing with funduscopic examination. The finding of fever with acute headache warrants additional maneuvers to elicit evidence of meningeal inflammation, such as a Kernig sign (a supine patient with hips flexed to 90 degrees who displays resistance or reports pain with passive extension of the knees) and Brudzinski sign (supine patient who reflexively flexes the hip and knees after the examiner passively flexes the neck). The absence of jolt accentuation of headache cannot accurately rule out meningitis. Patients older than 60 years should be examined for scalp or temporal artery tenderness.

Table 2-6. Summary LRs for individual clinical features associated with migraine diagnosis.

Clinical Feature	LR+ (95% Cl)	LR- (95% Cl)
Nausea	19 (15-25)	0.19 (0.18—-0.20)
Photophobia	5.8 (5.1-6.6)	0.24 (0.23-0.26)
Phonophobia	5.2 (4.5-5.9)	0.38 (0.36-0.40)
Exacerbation by physical activity	3.7 (3.4-4.0)	0.24 (0.23-0.26)

Table 2-7. SNNOOP10 list of “red” flags for secondary causes of headache.

Sign or Symptom
Systemic symptoms!

Neoplasm in history

Neurologic deficit/dysfunction

Onset of headache is sudden or abrupt

Older age (> 50 years)

Pattern change or recent onset of headache

Positional headache

Precipitated by sneezing, coughing, or exercise

Papilledema

Progressive headache and atypical presentations

Pregnancy or puerperium

Painful eye with autonomic features

Posttraumatic onset of headache

Immunosuppression, eg, HIV, immunosuppressive

Related Secondary Headaches

Headache attributed to infection, nonvascular intracranial disorders, carcinoid, or pheochromocytoma

Neoplasms of the brain; metastasis

Headaches attributed to vascular, nonvascular intracranial disorders; brain abscess and other infections

Subarachnoid hemorrhage and other headache attributed to cranial or cervical vascular disorders

Giant cell arteritis and other headache attributed to cranial or cervical vascular disorders; neoplasms and other nonvascular intracranial disorders

Neoplasms, headaches attributed to vascular, nonvascular intracranial disorders

Intracranial hypertension or hypotension

Posterior fossa malformations; Chiari malformation

Neoplasms and other nonvascular intracranial disorders; intracranial hypertension

Neoplasms and other nonvascular intracranial disorders

Headaches attributed to cranial or cervical vascular disorders; postdural puncture headache; hypertension-related disorders (eg, preeclampsia); cerebral sinus thrombosis; hypothyroidism; anemia; diabetes mellitus

Pathology in posterior fossa, pituitary region, or cavernous sinus; Tolosa-Hunt syndrome (severe, unilateral headaches with orbital pain and ophthalmoplegia due to extraocular palsies); other ophthalmic causes

Acute and chronic posttraumatic headache; subdural hematoma and other headache attributed to vascular disorders

Opportunistic infections

medications

Painkiller overuse or new drug at onset of headache

"Orange" flag for isolated fever alone.

Medication overuse headache; drug incompatibility

Reproduced with permission from Do TP et al. Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. Neurology.

2019;92(3):134-144. https://n.neurology.org/content/92/3/134.long

Careful assessment of visual acuity, ocular gaze, visual fields, pupillary defects, optic disks, and retinal vein pulsations is crucial. Diminished visual acuity is suggestive of glaucoma, temporal arteritis, or optic neuritis. Ophthalmoplegia or visual field defects may be signs of venous sinus thrombosis, tumor, or aneurysm. Afferent pupillary defects can be due to intracranial masses or optic neuritis. In the setting of headache and hypertension, retinal cotton wool spots, flame hemorrhages, and disk swelling indicate acute severe hypertensive retinopathy. Ipsilateral ptosis and miosis suggest Horner syndrome and in conjunction with acute headache may signify carotid artery dissection. Finally, papilledema or absent retinal venous pulsations are signs of elevated intracranial pressure—findings that should be followed by neuroimaging prior to performing lumbar puncture (Table 2-5). On nonmydriatic fundoscopy, up to 8.5% of patients who arrive at the emergency department complaining of headache had abnormalities; although few had

other significant physical examination findings, 59% of them had abnormal neuroimaging studies.

Complete neurologic evaluations are also critical and should include assessment of mental status, motor and sensory systems, reflexes, gait, cerebellar function, and pronator drift. Any abnormality on neurologic evaluation (especially mental status) warrants emergent neuroimaging (Table 2-5).

1. Neuroimaging indications—Indications for neuroimaging are listed in Table 2-5. Under most circumstances, a noncontrast head CT is sufficient to exclude intracranial hypertension with impending herniation, intracranial hemorrhage, and many types of intracranial masses (notable exceptions include lymphoma and toxoplasmosis in patients with HIV, herpes simplex encephalitis, and brain abscess). When needed, a contrast study can be ordered to follow a normal noncontrast study. A normal neuroimaging study does not exclude subarachnoid hemorrhage and should be followed by lumbar puncture. One study supported a change of practice wherein a lumbar puncture can be withheld when a head CT scan was performed less than 6 hours after headache onset and showed no evidence of subarachnoid hemorrhage (negative predictive value 99.9%).

In a prospective study of 1536 emergency department patients, the yield for acute findings on head CT differed based on the indications for imaging and were 27% for seizures, 20% for confusion, 19% for syncope, 16% for focal neurologic deficit, 15% for head injury, 12% for headache, and 8% for dizziness.

In patients for whom there is a high level of suspicion for subarachnoid hemorrhage or aneurysm, a normal CT

and lumbar puncture should be followed by angiography within the next few days (provided the patient is medically stable).

2. Lumbar puncture—This test is indicated to exclude infectious causes of acute headache, particularly in patients with fever or meningeal signs. CSF tests should routinely include Gram stain, WBC count with differential, RBC count, glucose, total protein, and bacterial culture. In appropriate patients, also consider testing cerebrospinal fluid for Venereal Disease Research Laboratory (syphilis), cryptococcal antigen (patients with HIV), acid-fast bacillus stain and culture, and complement fixation and culture for coccidioidomycosis. Storage of an extra tube with 5 mL of cerebrospinal fluid is prudent for conducting unanticipated tests in the immediate future. PCR tests for specific infectious pathogens (eg, herpes simplex 2) should be considered in patients with evidence of CNS infection but no identifiable pathogen.

The Ottawa subarachnoid hemorrhage clinical decision rule had 100% sensitivity (and 13-15% specificity in different studies) in predicting subarachnoid hemorrhage. According to it, patients who seek medical attention in an emergency department complaining of an acute nontraumatic headache should be evaluated for subarachnoid hemorrhage if they have one or more of the following factors: age 40 years or older, neck pain or stiffness, witnessed loss of consciousness, onset during exertion, thunderclap headache (instantly peaking pain), or limited neck flexion on examination.

In addition to neuroimaging and lumbar puncture, additional diagnostic tests for exclusion of life-threatening

causes of acute headache include ESR (temporal arteritis; endocarditis), UA (malignant hypertension; preeclampsia), and sinus CT (bacterial sinusitis, independently or as a cause of venous sinus thrombosis).

In patients in whom migraine or migraine-like headache has been diagnosed, early treatment with ketorolac (oral, nasal, or intramuscular), dihydroergotamine, lasmiditan, ubrogepant, or triptans (oral, nasal, subcutaneous) can often abort or provide significant relief of symptoms (see migraine headaches). Intravenous prochlorperazine plus diphenhydramine are more effective for migraine pain relief than intravenous hydromorphone in the emergency department. Prochlorperazine appears to be superior to ketamine for the treatment of migraine headaches (without signs or symptoms of serious intracranial pathology) in the emergency department. Sumatriptan may be less effective as immediate therapy for migraine attacks with aura compared to attacks without aura. Haloperidol (2.5 mg intravenously) given to patients in the emergency department with severe benign headache resulted in a significant reduction pain score compared with placebo. Although oral beta-blockers used for the prevention of migraine headache are not effective for the treatment of acute pain, timolol eye drops may be effective in the management of acute migraine pain.

There may be a role for oral corticosteroids to prevent a rebound migraine headache after emergency department discharge, but in one study, long-acting intramuscular methylprednisolone acetate did not decrease the frequency of post-emergency department discharge headache days compared with oral dexamethasone. Parenteral morphine

and hydromorphone are best avoided as first-line therapy, although opioids are still prescribed to nearly half of all patients with acute migraine.

Galcanezumab is an approved treatment for episodic cluster headache. High-flow oxygen therapy may provide effective treatment for all headache types in the emergency department setting (eg, benefitting older patients with cluster headaches).

A study found that metoclopramide plus diphenhydramine was more effective than placebo for acute post-traumatic headache (with 43% of the patients who received metoclopramide reporting adverse events).

« Frequent migraines not responsive to standard therapy.

« Migraines with atypical features.

* Chronic daily headaches due to medication overuse.

« Need for repeated doses of parenteral pain medication.

* To facilitate an expedited workup requiring a sequence of neuroimaging and procedures.

« To monitor for progression of symptoms and to obtain neurologic consultation when the initial emergency department workup is inconclusive.

« Pain severe enough to impair activities of daily living or impede follow-up appointments or consultations.

« Patients with subarachnoid hemorrhage, intracranial mass, or meningitis.

Bilello LA et al. Retrospective review of pregnant patients presenting for evaluation of acute neurologic complaints. Ann Emerg Med. 2021;77:210. [PMID: 32418678]

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=== DYSURIA ===

Fever; new back or flank pain; nausea or vomiting.
Vaginal discharge.
Pregnancy risk.
Structural abnormalities.
Instrumentation of urethra or bladder.
Dysuria (painful urination) is a common reason for adults and adolescents to seek urgent medical attention. An inflammatory process (eg, bacterial UTI, herpes simplex, autoimmune disorder) underlies most causes of dysuria. In women, cystitis is diagnosed in up to 50-60% of cases. Cystitis has an incidence of 0.5-0.7% per year in sexually active young women. The key objective in evaluating women with dysuria is to exclude serious upper urinary tract disease, such as acute pyelonephritis, and STIs. In

older men, dysuria may be a symptom of prostatitis; in younger men, urethritis accounts for most cases of dysuria. Male cyclists have no worse sexual or urinary functions than swimmers or runners, but cyclists are more prone to urethral stricture.

Well-designed cohort studies have shown that some cases of uncomplicated cystitis can be reliably diagnosed without a physical examination or UA, and RCTs show that telephone management of uncomplicated cystitis is safe and effective. An increased likelihood of cystitis is present when women report multiple irritative voiding symptoms (dysuria, urgency, frequency), fever, or back pain (positive LRs = 1.6-2.0). A cohort study found that the symptom of dysuria most reliably predicted a culture-positive UTI. Elderly patients with cognitive impairment may not have local urinary tract symptoms. A history of recurrent UTI is associated with a positive urine culture (recurrent UTI adjusted OR 2.45). Inquiring about symptoms of vulvovaginitis is imperative. When women report dysuria and urinary frequency, and deny vaginal discharge and irritation, the LR for culture-confirmed cystitis is 24.5. In contrast, when vaginal discharge or irritation is present, as well as dysuria or urinary frequency, the LR is 0.7. Gross hematuria in women with voiding symptoms usually represents hemorrhagic cystitis but can be a sign of bladder cancer (particularly in older patients) or upper tract disease. Failure of hematuria to resolve with antibiotic treatment should prompt further evaluation of the bladder and kidneys. Chlamydial infection should be strongly considered among women aged 25 years or younger who are sexually active and seeking medical attention for a sus-

pected UTI for the first time or who have a new sexual partner.

Fever, back pain, nausea, and vomiting are clinical criteria for acute pyelonephritis. Women with these symptoms should usually be examined before initiation of treatment to exclude coexistent urosepsis, hydronephrosis, or nephrolithiasis that would affect management decisions. Risk factors for acute pyelonephritis among women aged 18-49 years relate to sexual behaviors (frequent sexual intercourse [three times per week or more], new sexual partner in the previous year, recent spermicide use), as well as diabetes mellitus and recent UTI or incontinence.

Pregnancy, underlying structural factors (polycystic kidney disease, nephrolithiasis, neurogenic bladder), immunosuppression, diabetes mellitus, and a history of recent bladder or urethral instrumentation usually alter the treatment regimen (antibiotic choice or duration of treatment, or both) for cystitis. Presence of UTI during pregnancy is strongly associated with preeclampsia (particularly UTI during the third trimester).

Fever, tachycardia, or hypotension suggests urosepsis and potential need for hospitalization. A focused examination in women, in uncomplicated circumstances, can be limited to ascertainment of costovertebral angle tenderness as a finding for pyelonephritis and to a lower abdominal and pelvic examination if the history suggests vulvovaginitis or cervicitis.

1. Urinalysis—UA is probably overutilized in the evaluation of dysuria. The probability of culture-confirmed UTI among women with a history and physical examination

compatible with uncomplicated cystitis is about 70-90%. UA is most helpful in atypical presentations of cystitis. Dipstick detection (greater than trace) of leukocytes, nitrites, or blood supports a diagnosis of cystitis. When both leukocyte and nitrite tests are positive, the LR is 4.2, and when both are negative, the LR is 0.3.

The negative predictive value of UA is not sufficient to exclude culture-confirmed UTI in women with multiple and typical symptoms, and randomized trial evidence shows that antibiotic treatment is beneficial to women with typical symptoms and negative UA dipstick tests. Microscopy of unspun urine may also be helpful in diagnosis and reduces unnecessary use of antibiotics. The combination of urgency, dysuria, and pyuria assessed with the high-power (40x) objective for leukocytes (more than 1 leukocyte/7 high-power fields) had a positive predictive value of 71 and LR of 2.97. Urine samples produced at home rarely meet diagnostic standards.

2. Urine culture—Urine culture should be considered for all women with upper urinary tract symptoms (prior to initiating antibiotic therapy), as well as those with dysuria and a negative urine dipstick test. In symptomatic women, a clean-catch urine culture is considered positive when 107-10? colony-forming units/mL of a uropathogenic organism are detected. Urine culture sensitivity decreases rapidly after empiric antibiotic administration (75% of cultures were negative 9 hours after antibiotic treatment). Multiplex PCR analysis has been found to be as beneficial as a urine culture.

3. Renal imaging—When severe flank or back pain is present, the possibility of complicated kidney infection (peri-

nephric abscess, nephrolithiasis) or of hydronephrosis should be considered. Renal ultrasound or CT scanning should be done to rule out abscess and hydronephrosis. To exclude nephrolithiasis, noncontrast helical CT scanning is more accurate than renal ultrasound and is the diagnostic test of choice. In a meta-analysis, the positive and negative LRs of helical CT scanning for diagnosis of nephrolithiasis were 23.2 and 0.05, respectively.

The differential diagnosis of dysuria in women includes acute cystitis, acute pyelonephritis, vaginitis (Candida, bacterial vaginosis, Trichomonas, herpes simplex), urethritis/cervicitis (Chlamydia, gonorrhea), and interstitial cystitis/painful bladder syndrome. Pelvic congestion syndrome (dilated and refluxing pelvic veins) may also cause dysuria and pelvic pain.

Nucleic acid amplification tests from first-void urine or vaginal swab specimens are highly sensitive for detecting chlamydial infection in men and women. Other infectious pathogens associated with dysuria and urethritis in men include Mycoplasma genitalium and Enterobacteriaceae.

Definitive treatment is directed to the underlying cause of the dysuria. An evidence-informed algorithm for managing suspected UTI in women is shown in Figure 2-1. This algorithm supports antibiotic treatment of most women with multiple and typical symptoms of UTI without performing UA or urine culture. Telemedicine may be an appropriate technology to assess and manage uncomplicated UTI for average-risk patients who can self-diagnose. Antibiotic selection should be guided by local resistance patterns and expert-panel clinical practice guidelines; major options for uncomplicated cystitis include nitrofurantoin, fosfomycin,

ciprofloxacin, and trimethoprim-sulfamethoxazole. Five days of nitrofurantoin results in a significantly greater likelihood of clinical and microbiologic resolution than single-dose fosfomycin.

In a study of 47 patients with UTIs due to multidrug-resistant bacteria, treatment with fosfomycin resulted in clinical cure rates of 87% and 94% at 48 hours and 14 days, respectively.

According to the American Academy of Pediatrics' Committee on Drugs, antibiotics that are usually acceptable when treating women who are breastfeeding include trimethoprim-sulfamethoxazole (unless G6PD deficiency is present), amoxicillin, nitrofurantoin, ciprofloxacin, and ofloxacin. Plazomicin, a novel neoglycoside, is FDA approved for the treatment of adults with complicated UTIs who have limited or no alternative treatment options.

In men, prolonged treatment of UTIs (more than 7 days) out of concern for delayed clearance of infection within the prostate does not appear to reduce early or late recurrences. A 5-day course of fluoroquinolones for outpatient men with UTI is as effective as a 10-day course.

Among afebrile men with symptoms of UTI, treatment with ciprofloxacin or trimethoprim/sulfamethoxazole for 7 days was noninferior to 14 days regarding resolution of UTI symptoms.

Symptomatic relief can be provided with phenazopyridine, a urinary analgesic that is available over the counter; it is used in combination with antibiotic therapy (when a UTI has been confirmed) but for no more than 2 days. Patients should be informed that phenazopyridine will cause orange/red discoloration of their urine and other

body fluids (eg, some contact lens wearers have reported discoloration of their lenses). Rare cases of methemoglobinemia and hemolytic anemia have been reported, usually with overdoses or underlying kidney dysfunction. NSAIDs have also been shown to be of symptomatic benefit, but less effective than antibiotic therapy. Although some women recover from uncomplicated UTI when treated with NSAIDs alone (53% in a Norwegian study), the rate of progression to pyelonephritis was substantial. Delayed antibiotic therapy in elderly patients with UTI leads to a substantially higher rate of urosepsis and all-cause mortality. If a broad-spectrum antibiotic was initially prescribed empirically for UTI and urine culture results return establishing efficacy of a narrow-spectrum antibiotic, treatment should be "de-escalated" to the narrow-spectrum antimicrobial. Among premenopausal women with recurrent UTIs, the group with increased daily water consumption had a lower mean number of cystitis episodes over a 12-month period of 1.7 compared with 3.2 in the control group and reduced number of antibiotic prescriptions (1.9 and 3.6, respectively). A systematic review and meta-analysis found D-mannose protective against recurrent UTIs, but there are few high-quality RCTs testing this therapy. In patients with asymptomatic renal calculi and recurrent UTIs, stone extraction eliminated infections in 50% of women.

In cases of interstitial cystitis/painful bladder syndrome modal approach that may include urethral/vesicular dilation, biofeedback, cognitive-behavioral therapy, antidepressants, dietary changes, vaginal emollients, and other supportive measures. Vaginal estrogen effectively

relieves urinary urgency and frequency as well as recurrent UTIs related to vulvovaginal atrophy of menopause (also known as genitourinary syndrome of menopause).

Asymptomatic bacteriuria—The incidence of asymptomatic bacteriuria increases with age and may be more than 15% in women older than age 80 (50% for those who reside in long-term care facilities). A meta-analysis found that antibiotic treatment for most people with asymptomatic bacteriuria is not beneficial and may be harmful.

Eligible woman between the ages of 18 and 55 telephones or presents to clinic with predominant symptoms of dysuria or urinary urgency; she suspects she has a UTI.

exclusion criteria??

Does the patient request an office visit?

=== ' Y ===

Does patient meet any of the J_"*S___,| atient excluded from the pathway

Patient offered the option of either an Office visit with a health care provider Yes

or telephone management. [> Schedule visit with a health care provider’

Prescribe one from the following list:

1. Nitrofurantoin monohydrate/macrocrystals (100 mg orally twice daily for 5 days); or

2.Fosfomycin tromethamine (3 g orally once); or

3. Ciprofloxacin (250 mg orally twice daily for 3 days); or

4. Trimethoprim-sulfamethoxazole double-strength (orally twice daily for 3 days)

1Primary exclusion criteria include documented fever 38°C or greater; symptoms of dysuria or urgency

27 days; symptoms of vaginitis are present; abdominal pain, nausea, or vomiting; gross hematuria in patients

older than 50 years; immunosuppression (eg, current use of chemotherapeutic agents); diabetes mellitus;

known pregnancy; chronic renal or urologic abnormalities, other than stress urinary incontinence (eg, polycystic

kidney disease, neurogenic bladder, renal failure); recent or persistent urinary stones; urinary catheterization or

other urologic procedure < 2 wk ago; discharge from hospital or nursing home < 2 wk ago; treatment for

UTI s 2 wk ago; recurrent symptomatic UTI.

4 Figure 2-1. Proposed algorithm for evaluating women with symptoms of acute UTI. (Data from Gupta K et al;

Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical

practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by

the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect

Dis. 2011;52:e103.)

Antibiotic treatment does benefit both pregnant women

with asymptomatic bacteriuria as well as persons about to

undergo urologic surgery. The USPSTF recommends

screening pregnant women for asymptomatic bacteriuria

by obtaining a urine culture (B recommendation). The

USPSTF recommends against screening for asymptomatic

bacteriuria in nonpregnant adults (D recommendation).

Urine WBC count greater than 25 cells/high power field

was associated with a 53.8% rate of bacteriuria in a study of

46,127 adult inpatients and is suggested to be the optimal

“cutoff” value.

There were no differences in the prevalence of postop-

erative UTI in women who had mixed flora on preoperative urine cultures compared to those with no growth on preoperative urine cultures.

Anatomic abnormalities leading to repeated urinary infections.

Infections associated with nephrolithiasis.

Persistent interstitial cystitis/painful bladder syndrome.

Severe pain requiring parenteral medication or impairing ambulation or urination (such as severe primary herpes simplex genitalis).

Dysuria associated with urinary retention or obstruction.

Pyelonephritis with ureteral obstruction.

Symptoms and signs suggesting urosepsis.