SECTION 8

Pulmonary Disorders

CHAPTER 62

Respiratory Distress

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GENERAL APPROACH TO RESPIRATORY DISTRESS

INTRODUCTION

Dyspnea is a subjective feeling of difficult, labored, or uncomfortable breathing, which patients often describe as "shortness of breath," "breathlessness," or "not getting enough air."[1] Dyspnea is frequently associated with other respiratory symptoms or signs. **Tachypnea** is rapid breathing. **Orthopnea** is dyspnea in the recumbent position. It is most often the result of left ventricular failure, but can also be seen with diaphragmatic paralysis or chronic obstructive pulmonary disease. **Paroxysmal nocturnal dyspnea** is orthopnea that awakens the patient from sleep, prompting an upright posture in order to resolve breathlessness. **Trepopnea** is dyspnea associated with only one of several recumbent positions. Trepopnea can occur with unilateral diaphragmatic paralysis, with ball-valve airway obstruction, or after surgical pneumonectomy. **Platypnea** is the opposite of orthopnea: dyspnea in the upright position. Platypnea results from the loss of abdominal wall muscular tone and, in rare cases, from right-to-left intracardiac shunting, as occurs from a patent foramen ovale. **Hyperpnea** is essentially hyperventilation and is defined as minute ventilation in excess of metabolic demand. **Respiratory distress** is a term used by the physician, combining the patient's subjective sensation of dyspnea with signs indicating difficulty breathing. **Ventilatory or respiratory failure** occurs when the lungs and ventilatory muscles cannot move enough air in and out of the alveoli to adequately oxygenate arterial blood and eliminate carbon dioxide.

PATHOPHYSIOLOGY

Dyspnea is a complex sensation that arises from the interaction of multiple pathophysiologic mechanisms.[1,2] Sensory information about respiratory activity generated by multiple afferent receptors is integrated within the CNS at both the subcortical and cortical levels. The current explanation for the sensation of dyspnea is when imbalance exists among the inspiratory drive, efferent activity to the respiratory muscles, and feedback from these afferent receptors.

CLINICAL FEATURES

Dyspnea is a feature of several disorders seen in the ED (**Table 62-1**). The presence or degree of dyspnea is difficult to measure, although categorical scales (e.g., the Borg or Fletcher scales) and visual analog scales can be used to gauge response to therapy.[1,3] Assess for evidence of impending respiratory failure: marked tachypnea and tachycardia; stridor; use of the accessory respiratory muscles, including the sternocleidomastoid, sternoclavicular, and intercostals; inability to speak normally as a consequence of breathlessness; agitation or lethargy as a consequence of hypoxemia; depressed consciousness due to hypercapnia; and paradoxical abdominal wall movement when the abdominal wall retracts inward with inspiration, indicating diaphragmatic fatigue. In patients with these signs, give oxygen and be prepared for more advanced measures (discussed elsewhere). Lesser degrees of dyspnea allow for a more detailed medical history, physical examination, and indicated ancillary tests.

DIAGNOSIS

Ask about recent infectious and environmental exposures that may impair respiratory function. Carefully question patients who require daily medications for symptom control about compliance and possible drug interactions.

Dyspnea is a prominent symptom of heart failure,[4] and differentiating heart failure from pulmonary causes of dyspnea is an important and frequently difficult task. Treatment and prognosis differ, and embarking down the wrong pathway of treatment can have adverse consequences.[5] Several findings can assist in this differentiation, although few of them are definitive by themselves (**Table 62-2**).[6-8]

An S_3 gallop on physical examination or pulmonary venous congestion/interstitial edema (especially with concomitant cardiomegaly) on chest x-ray strongly suggest heart failure as the cause of the dyspnea (**Figure 62-1**).[6] The physician's overall gestalt of the diagnosis, the presence of jugular venous distention on examination, and alveolar edema on chest x-ray suggest heart failure. Wheezing, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and leg edema are not useful in discriminating between cardiac and pulmonary causes. Conversely, the absence of these findings does not exclude heart failure.

LABORATORY TESTING AND IMAGING

Pulse oximetry provides a rapid assessment of arterial oxygen saturation but is an insensitive screening test for disorders of gas exchange. Arterial blood gas analysis is more sensitive for detecting impaired gas exchange but cannot evaluate the work of breathing. Arterial blood gas testing can find the rare patient with dyspnea or tachypnea who exhibits no evidence of hypoxemia or pulmonary disease, suggesting hyperventilating from metabolic acidosis.

Bedside spirometric analysis (e.g., peak expiratory flow), especially if performed before and after bronchodilator therapy, can be used to diagnose dyspnea resulting from asthma or chronic obstructive pulmonary disease, but spirometry requires voluntary effort that might be difficult for dyspneic patients.

Negative inspiratory force can assess strength of the diaphragm and inspiratory muscles. Other potentially useful tests include an ECG and measuring the hemoglobin level. In most ED patients, the cause of dyspnea can be identified by the history, the physical examination, and these ancillary tests.

B-type natriuretic peptide (BNP) is a polypeptide secreted by ventricular myocytes in response to volume expansion and pressure overload; BNP elevates with any cause of overload, including heart failure, myocardial ischemia, pulmonary embolism, sepsis, chronic obstructive pulmonary disease, or any right heart strain. Serum levels of BNP or its precursor, N-terminal pro-BNP, are measured using two methods: an enzyme-linked immunosorbent assay and a radioimmunoassay; the enzyme-linked immunosorbent assay is more accurate than the radioimmunoassay.[9]

A normal BNP (<100 picograms/mL) or N-terminal pro-BNP (<500 picograms/mL) excludes heart failure in low and moderate pretest probability patients outside of "flash" settings.[6,9,10] A high level (BNP >500 picograms/mL or N-terminal pro-BNP >2000 picograms/mL)

TABLE 62-1 Common Causes of Dyspnea in the ED

Most Common Causes	Most Immediately Life-Threatening Causes
Obstructive airway disease: asthma, chronic obstructive pulmonary disease	Upper airway obstruction: foreign body, angioedema, hemorrhage
Decompensated heart failure/ cardiogenic pulmonary edema	Tension pneumothorax
Ischemic heart disease: unstable angina and myocardial infarction	Pulmonary embolism
Pneumonia	Neuromuscular weakness: myasthenia gravis, Guillain-Barré syndrome, botulism
Psychogenic	Fat embolism

is moderately useful for establishing the diagnosis of heart failure, although these elevations are rarely unsuspected after a careful history, exam, and chest radiograph.[10,11] Overall, BNP measurement offers limited real help in assessing dyspneic patients,[12] especially when values between 100 and 500 picograms/mL occur, which is common in the patient without a clear clinical syndrome.[11,13,14]

A chest radiograph may find a pulmonary abnormality, infiltrate, effusion, and pneumothorax.

Bedside lung US is an important tool in the assessment of acute dyspnea. It can differentiate acute decompensated heart failure from noncardiac causes of acute dyspnea with a sensitivity and specificity of about 97% and is superior to chest x-ray and natriuretic peptide determination.[15,16] Bedside US can identify pleural effusion, pneumothorax, cardiac tamponade, cardiac functional abnormalities, pulmonary consolidation, and intravascular volume status (**Figures 62-2 to 62-4**).[17,18]

TREATMENT

In severe dyspnea, the initial treatment goal is maintenance of the airway and oxygenation, seeking a partial pressure of alveolar oxygen (Pao_2) > 60 mm Hg and/or arterial oxygen saturation (Sao_2) ≥90%. Next, or in those with lesser dyspnea, treat the underlying disorder. Rarely are opioids or benzodiazepines used as dyspnea therapy, except in near terminal states for patient comfort.[1,19]

TABLE 62-2 Factors Supporting Heart Failure as the Cause of Dyspnea[6]

Finding	LR+ (95% CI)	LR– (95% CI)
Clinical gestalt	4.4 (1.8–10.0)	0.45 (0.28–0.73)
History		
Heart failure	5.8 (4.1–8.0)	0.45 (0.38–0.53)
Myocardial infarction	3.1 (2.0–4.9)	0.69 (0.58–0.82)
Coronary artery disease	1.8 (1.1–2.8)	0.68 (0.48–0.96)
Symptoms		
Paroxysmal nocturnal dyspnea	2.6 (1.5–4.5)	0.70 (0.54–0.91)
Orthopnea	2.2 (1.2–3.9)	0.65 (0.45–0.92)
Edema	2.1 (0.92–5.00)	0.64 (0.39–1.10)
Dyspnea on exertion	1.3 (1.2–1.4)	0.48 (0.35–0.67)
Physical examination		
S_3 gallop	11.0 (4.9–25.0)	0.88 (0.83–0.94)
Jugular venous distention	5.1 (3.2–7.9)	0.66 (0.57–0.77)
Hepatojugular reflex	6.4 (0.81–51.00)	0.79 (0.62–1.00)
S4	1.6 (0.47–5.50)	0.98 (0.93–1.00)
Wheezing	0.52 (0.38–0.71)	1.3 (1.1–1.7)
Chest x-ray		
Pulmonary venous congestion	12.0 (6.8–21.0)	0.48 (0.28–0.83)
Interstitial edema	12.0 (5.2–27.0)	0.68 (0.54–0.85)
Alveolar edema	6.0 (2.2–16.0)	0.95 (0.93–0.94)
Cardiomegaly	3.3 (2.4–4.7)	0.33 (0.23–0.48)
ECG		
Atrial fibrillation	3.8 (1.7–8.8)	0.79 (0.65–0.96)
Any abnormal finding	2.2 (1.6–3.1)	0.64 (0.47–0.88)

Abbreviations: CI = confidence interval; LR = likelihood ratio.

FIGURE 62-1. Pulmonary edema. Cardiomegaly is present, the pulmonary vasculature is engorged, and cephalization of flow is present.

HYPOXIA AND HYPOXEMIA

Hypoxia is insufficient delivery of oxygen to the tissues. The amount of oxygen available to the tissues is a function of the arterial oxygen content (Cao_2) comprising a small portion dissolved in plasma and a larger portion bound to Hb:

$$Cao_2 = 0.0031 \times Pao_2 + 1.38 \times Hb \times Sao_2 \qquad \textbf{[Formula 1]}$$

Oxygen delivery (Do_2) is a product of arterial oxygen content and cardiac output (CO):

$$Do_2 = Cao_2 \times CO \qquad \textbf{[Formula 2]}$$

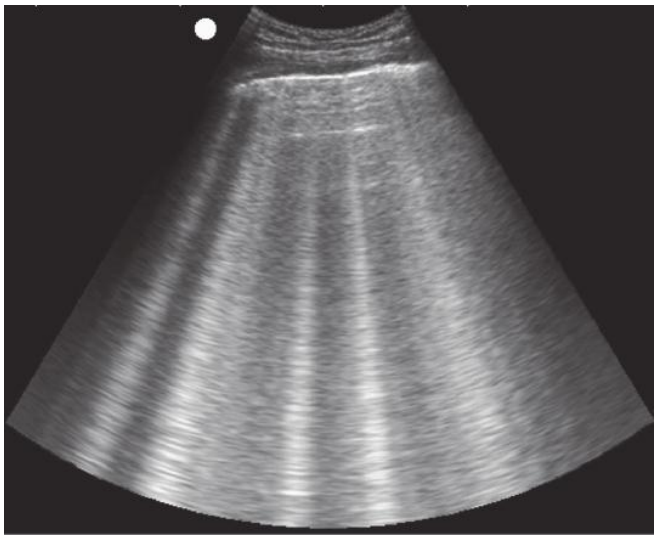


FIGURE 62-2. B lines of pulmonary edema. [Reproduced with permission from Silva FR, Mills L: Chapter 7. Pulmonary, in Ma OJ, Mateer JR, Reardon RF, et al (eds): *Ma and Mateer's Emergency Ultrasound*, 3rd ed. New York: McGraw-Hill Education; 2014. Fig. 7-4, Part B, p. 176.]

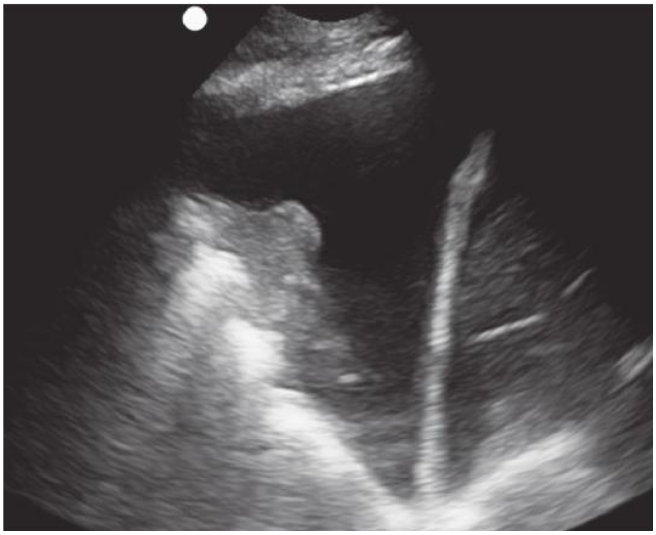


FIGURE 62-3. Pleural effusion. [Reproduced with permission from Silva FR, Mills L: Chapter 7. Pulmonary, in Ma OJ, Mateer JR, Reardon RF, et al (eds): *Ma and Mateer's Emergency Ultrasound*, 3rd ed. New York: McGraw-Hill Education; 2014. Fig. 7-4, Part D, p. 177.]

Tissue hypoxia occurs in states of low cardiac output, low Hb concentration, or low SaO_2. The level of oxygen saturation in arterial Hb is, in turn, dependent on the PaO_2, as determined by the oxygen-Hb dissociation curve. **Hypoxemia** is an abnormally low arterial oxygen tension (defined as a PaO_2 <60 mm Hg). While hypoxemia is the most common cause of hypoxia, *hypoxia* and *hypoxemia* are not interchangeable; one can occur without the other. For example, in states of low PaO_2 (hypoxemia) with concomitant polycythemia, the patient may have no tissue hypoxia. Alternatively, severely anemic patients may suffer tissue hypoxia despite a normal PaO_2.

Relative hypoxemia is the term used when the arterial oxygen tension is lower than expected for a given level of inhaled oxygen. The degree of relative hypoxemia can be assessed by calculating the alveolar arterial (A-a) oxygen partial pressure gradient, [$P(A\text{-}a)O_2$], which measures efficiency of oxygen transfer from the lungs to the circulation. Alveolar oxygen partial pressure is determined by the inhaled oxygen concentration (21% for room air), atmospheric pressure (760 mm Hg at sea level), and displacement by water vapor (47 mm Hg for full saturation) and carbon dioxide (CO_2). Gas in the alveolus is fully saturated with water vapor, and the amount of alveolar oxygen is further reduced by CO_2 that freely diffuses from the pulmonary capillaries in an amount determined by the ratio between oxygen consumption and CO_2 production, termed the *respiratory quotient* (R), which is affected by diet. On a typical mixed diet, the R is 0.8. Alveolar oxygen breathing room air at sea level has a:

$$PAO_2 = 0.21 \times (760 - 47) - PaCO_2/0.8 \qquad \textbf{[Formula 3]}$$

The A-a gradient at sea level for room air is a:

$$P(A\text{-}a)O_2 = 149 - PaCO_2/0.8 - PaO_2 \qquad \textbf{[Formula 4]}$$

A simplified formula often used is:

$$P(A\text{-}a)O_2 = 145 - PaCO_2 - PaO_2 \qquad \textbf{[Formula 5]}$$

A normal $P(A\text{-}a)O_2$ is <10 mm Hg in young, healthy patients and increases with age, predicted by the formula:

$$\mathbf{P(A\text{-}a)O_2 = 2.5 + 0.21\ (age\ in\ years)\ (\pm\ 11)} \qquad \textbf{[Formula 6]}$$

This normal A-a gradient is for healthy, asymptomatic individuals measured in an upright or sitting position. The supine position alone, as well as many chronic cardiac or pulmonary diseases, may raise the A-a gradient. The supine position is a common ED patient position, impairing the assessment.

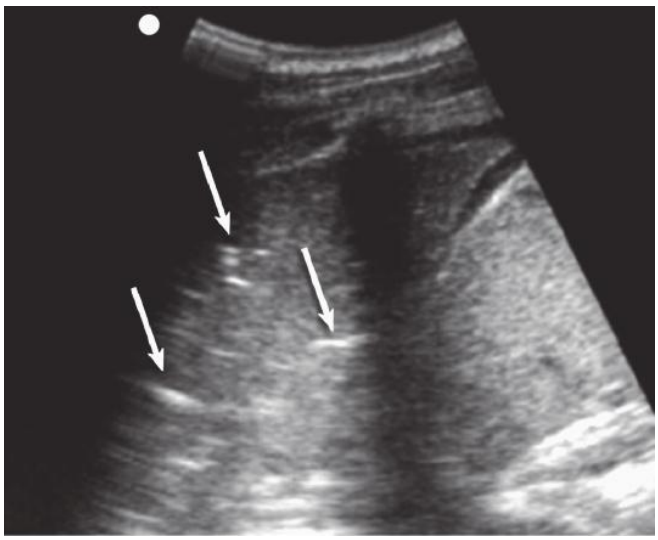


FIGURE 62-4. *Arrows* point to areas of pulmonary consolidation. [Reproduced with permission from Silva FR, Mills L: Chapter 7. Pulmonary, in Ma OJ, Mateer JR, Reardon RF, et al (eds): *Ma and Mateer's Emergency Ultrasound*, 3rd ed. New York: McGraw-Hill Education; 2014. Fig. 7-4, Part C, p. 177.]

PATHOPHYSIOLOGY

Hypoxemia results from any combination of five mechanisms.

1. *Hypoventilation.* Hypoxemia from hypoventilation alone has an increased $PaCO_2$ and a normal A-a O_2 gradient. The additional CO_2 displaces inhaled oxygen in the alveolus. However, the remaining alveolar oxygen diffuses and mixes normally into the arterial blood, displaying a normal A-a O_2 gradient as long as there is no alveolar or interstitial disease.
2. *Right-to-left shunt.* Right-to-left shunting occurs when blood enters the systemic circulation without traversing ventilated lung. There is always a small degree of right-to-left shunting because of the direct left atrial return of deoxygenated blood from both the coronary veins and the bronchial arteries. Increased right-to-left shunting occurs in a variety of conditions, including congenital cardiac malformation and acquired pulmonary disorders (pulmonary consolidation, pulmonary atelectasis). Regardless of the specific cause of the right-to-left shunt, it is always associated with an increase in the A-a O_2 gradient. **A hallmark of significant right-to-left shunting is the failure of arterial oxygen levels to increase in response to supplemental oxygen.** Although a small improvement may be observed with supplemental oxygen, hypoxemia is never fully eliminated because of the mixing of deoxygenated blood in the systemic circulation.
3. *Ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch.* Ideal pulmonary gas exchange depends on a balance of ventilation and perfusion. Any abnormality resulting in a regional alteration of either ventilation or perfusion can adversely affect pulmonary gas exchange, resulting in hypoxemia. There are many causes of $\dot{V}/\dot{Q}$ mismatch, including pulmonary emboli, pneumonia, asthma, chronic obstructive pulmonary disease, and even extrinsic vascular compression. Regardless of cause, hypoxemia from ventilation-perfusion mismatch is associated with an increased A-a O_2 gradient, and hypoxemia improves with supplemental oxygen.

4. *Diffusion impairment.* Pulmonary gas exchange requires diffusion across the alveolar–blood barrier. Regardless of the specific cause of the diffusion impairment, the A-a O_2 gradient is increased, and hypoxemia improves with supplemental oxygen.
5. *Low inspired oxygen.* Decreased ambient oxygen pressure results in hypoxemia. This is commonly seen at high altitude (including commercial air travel) or in nonobstructive asphyxia. The A-a O_2 gradient is normal, and hypoxemia improves with supplemental oxygen. For example, Denver, at 5400 ft (1646 m) above sea level, has an atmospheric pressure of 620 mm Hg and an inhaled P_{O_2} of only 0.21 × 620 = 130 mm Hg, as opposed to 160 mm Hg at sea level.

There are three distinct acute compensatory mechanisms for hypoxemia. Initially, minute ventilation increases. Next, pulmonary arterial vasoconstriction decreases perfusion to hypoxic alveoli. Although vasoconstriction balances ventilation and perfusion to restore arterial oxygenation, it may also cause acute right heart failure and is ineffective with diffuse lung disease. Finally, sympathetic tone increases and improves oxygen delivery by increasing cardiac output, usually with an increased heart rate. Chronic compensatory mechanisms include an increased red blood cell mass and decreased tissue oxygen demands. These compensatory mechanisms appear to be activated at different levels of hypoxemia among different individuals. However, the acute compensatory mechanisms are always activated when Pa_{O_2} reaches 60 mm Hg, and compensatory mechanisms fail when Pa_{O_2} falls below 20 mm Hg.

CLINICAL FEATURES

The signs and symptoms of hypoxemia are nonspecific. CNS manifestations include agitation, headache, somnolence, coma, and seizures. Although tachypnea and hyperventilation are often present, by the time Pa_{O_2} is <20 mm Hg, there is a central depression of respiration. **Cyanosis, the blood or tissue discoloration associated with a lowered arterial oxygenation saturation, is not a sensitive or specific indicator of hypoxemia.** Patients with chronic compensatory mechanisms may display polycythemia or alterations in body habitus (e.g., pulmonary cachexia).

DIAGNOSIS AND TREATMENT

Hypoxemia is defined as a Pa_{O_2} <60 mm Hg, so formal diagnosis requires arterial blood gas analysis. Although pulse oximetry is useful for screening purposes and decreased Sa_{O_2} readings accurately predict significant hypoxemia, clinically acceptable pulse oximetry saturation readings (>90%) do not exclude hypoxemia. If certain hemoglobin abnormalities exist (e.g., methemoglobin or carboxyhemoglobin), pulse oximetry analysis may overestimate oxygen saturation and under measure the response to supplemental oxygen (see the section "Cyanosis," below). Regardless of the specific cause of hypoxemia, the initial approach remains the same: ensuring a patent airway and providing supplemental oxygenation with a goal of maintaining a Pa_{O_2} >60 mm Hg. **Except in patients with right-to-left shunts, arterial oxygenation responds to supplemental oxygen.**

HYPERCAPNIA

Hypercapnia is exclusively caused by alveolar hypoventilation and is defined as a Pa_{CO_2} >45 mm Hg. Alveolar hypoventilation has many causes, including rapid shallow breathing, small tidal volumes, underventilation of the lung, or reduced respiratory drive. **Hypercapnia never results from increased CO_2 production alone (Table 62-3).**

PATHOPHYSIOLOGY

A portion of each tidal volume remains in the non–gas-exchange portion of the respiratory system—termed the *dead space*—that is determined by the anatomic size of the conducting airways (trachea and bronchi). The portion of the tidal volume that reaches the alveoli is that which remains after the dead space volume is subtracted:

TABLE 62-3 Causes of Hypercapnia

Depressed central respiratory drive
Structural CNS disease: brainstem lesions
Drug depression of respiratory center: opioids, sedatives, anesthetics
Endogenous toxins: tetanus
Thoracic cage disorders
Kyphoscoliosis
Morbid obesity
Neuromuscular impairment
Neuromuscular disease: myasthenia gravis, Guillain-Barré syndrome
Neuromuscular toxin: organophosphate poisoning, botulism
Intrinsic lung disease associated with increased dead space
Chronic obstructive pulmonary disease
Upper airway obstruction

$$Ta \text{ (alveolar volume)} = V_T \text{ (tidal volume)} - Td \text{ (dead space)} \quad \textbf{[Formula 7]}$$

Alveolar ventilation (V_A) per minute is the alveolar volume multiplied by the respiratory rate:

$$V_A = Ta \times R = (V_T - Td) \times R \quad \textbf{[Formula 8]}$$

Alveolar hypoventilation can result from a decrease in respiratory rate, a decrease in V_T, or an increase in dead space. Dead space volume can increase above that due to the anatomic size of the conducting airways, such as seen as a result of ventilation of lung portions with deficient or absent perfusion; these ventilated portions do not participate fully in gas exchange because of inadequate blood flow.

Medullary chemoreceptors stimulate both respiratory rate and V_T in response to increased CO_2, so that alveolar ventilation is finely controlled relative to CO_2 production and Pa_{CO_2} is maintained within a narrow range. Decreased respiratory drive is associated with CNS lesions and toxic depression (Table 62-3). Thoracic cage and neuromuscular disorders produce hypoventilation by slowing respiratory rate and/or decreasing V_T relative to the production of CO_2. Intrinsic lung diseases, such as chronic obstructive pulmonary disease, produce alveolar hypoventilation because of an increase in dead space.

CLINICAL FEATURES

The signs and symptoms of hypercapnia depend on the absolute value of Pa_{CO_2} and its rate of change. Acute elevations result in increased intracranial pressure, and patients may complain of headache, confusion, or lethargy. Severe hypercapnia can produce seizures and coma. Extreme hypercapnia can result in cardiovascular collapse, but this is usually seen only with acute elevations of Pa_{CO_2} >100 mm Hg. As opposed to acute hypercapnia, chronic hypercapnia, even >80 mm Hg, may be well tolerated.

DIAGNOSIS

Diagnosis of hypercapnia requires arterial blood gas analysis, and pulse oximetry assessment can be normal. With acute hypercapnia, the serum bicarbonate level increases slightly as a result of mass action through the CO_2–bicarbonate (HCO_3^-) equilibrium: HCO_3^- increases about 1 mEq/L for each increase of 10 mm Hg in the Pa_{CO_2}. Patients with chronic hypercapnia have an elevated serum HCO_3^- concentration and normal pH due to the renal retention of bicarbonate in response to increased Pa_{CO_2}: the serum HCO_3^- concentration increases about 3.5 mEq/L for each increase of 10 mm Hg in the Pa_{CO_2}.

TREATMENT

Hypercapnia is treated by increasing minute ventilation, both the respiratory rate and the VT, as appropriate. This involves ensuring a patent airway and may require noninvasive ventilation, mechanical ventilation, the use of an antidote to reverse drug toxicity, or, rarely, the use of a respiratory stimulant such as doxapram.[20] **Do not withhold oxygen required to maintain minimum saturation levels in any chronic lung disease patient in an effort to stimulate ventilation and reduce hypercapnia.**

The disposition of hypercapnic patients depends primarily on the underlying cause and severity. In general, patients with hypercapnia with new acidosis or that causes CNS symptoms should be hospitalized. Also, patients with neuromuscular disease—either congenital or acquired—who present with acute hypercapnia should be hospitalized. Some chronic obstructive pulmonary disease patients have chronic hypercapnia and do not require admission provided they are stable. Conversely, patients with chronic obstructive pulmonary disease who display worsening hypercapnia despite maximal outpatient therapy require hospital admission.

WHEEZING

Wheezes are "musical" adventitious lung sounds produced by airflow through the central and distal airways.[21] The duration is prolonged, typically >80 milliseconds. Wheezes differ from the other two main adventitial lung sounds: rhonchi and crackles (rales). Rhonchi are a series of damped sinusoidal sounds of lower frequency (<300 Hz) and prolonged duration (>100 milliseconds). Crackles or rales are a series of intermittent individual sounds, typically <20 milliseconds in duration. Wheezing is usually more prominent on exhalation, in contrast to upper airway stridor, which is more prominent during inspiration.

The current theory is that wheezes are produced by airway flutter and vortex shedding from the central and distal airways, although movement of airway secretions may play a small role. Airway obstruction comes from bronchial smooth muscle contraction (bronchospasm), smooth muscle hypertrophy, increased mucus secretion, and peribronchial inflammation.

Wheezing is usually associated lower airway disease such as with asthma or other obstructive pulmonary diseases with muscular spasm and inflammation (**Table 62-4**). Upper airway obstruction causes stridor, which is loudest during inspiration. An occasional wheeze is normal during forced expiration in some normal children and adults, and conversely, patients with severe airflow obstruction may not have audible wheezes.

Diagnosis and treatment of the different causes of wheezing are discussed in specific chapters in the Adult and Pediatric sections of this book. Treatment of wheezing is directed to the underlying disorder.

TABLE 62-4 Differential Diagnosis of Wheezing

Upper airway (more likely to be stridor, may be hard to separate from wheezing)
Angioedema: allergic, angiotensin-converting enzyme inhibitor, idiopathic
Foreign body
Infection: croup, epiglottis, tracheitis
Lower airway
Asthma
Transient airway hyperreactivity (usually caused by infection or irritation)
Bronchiolitis
Chronic obstructive pulmonary disease
Foreign body
Cardiovascular
Cardiogenic pulmonary edema ("cardiac asthma")
Noncardiogenic pulmonary edema (acute respiratory distress syndrome)
Pulmonary embolus (rare)
Psychogenic

COUGH

Cough is a protective reflex for clearing secretions and foreign debris from the tracheobronchial tree.[22] Coughing is initiated by stimulation of irritant receptors located largely in the larynx, trachea, and major bronchi. These receptors are stimulated by inhaled irritants (e.g., dust), allergens (e.g., ragweed pollen), toxic substances (e.g., gastric acid), hypo- or hyperosmotic liquids, inflammation (e.g., asthma), cold air, instrumentation, and excess pulmonary secretions. Minor cough receptors located in the upper respiratory tract (sinuses and pharynx) and chest (pleura, pericardium, and diaphragm) may stimulate coughing. Signals from these receptors travel by means of the vagus, phrenic, and other nerves to the cough center in the medulla.

Once stimulated, the cough center initiates the stereotypical cough pattern: a deep inspiration followed by attempted expiration against a closed glottis that suddenly opens, providing for a forceful exhalation of gas, secretions, and foreign debris from the tracheobronchial tree. The coughing sound is generated at the larynx and resonates in the nasal cavity and the lungs.

CLINICAL FEATURES

Acute cough is cough lasting <3 weeks and is usually associated with self-limited infectious upper respiratory or bronchial infections (Table 62-5).[23] Subacute cough lasts 3 to 8 weeks and is most commonly postinfectious, but causes of subacute cough overlap with causes of acute and chronic cough. **Chronic cough is cough present for >8 weeks.**[23]

ACUTE COUGH

Acute cough is most often caused by upper respiratory tract infection, lower respiratory tract infection, and allergic reactions.[23] Common upper respiratory infections are associated with a combination of rhinorrhea, sinusitis, pharyngitis, and laryngitis, with the cough a result of drainage from the nasopharynx onto cough receptors in the pharynx and larynx. A productive cough is the hallmark of acute bronchitis. Although pneumonia generally produces a cough, pulmonary secretions may be scant and the cough nonproductive. Pertussis in adults has been associated with acute cough lasting 1 to 6 weeks.[24] The observed increased incidence of pertussis in adolescents and young adults is thought to be due to waning vaccine immunity with increasing age.

SUBACUTE COUGH

Postinfectious cough is the most likely cause of subacute cough. The mechanisms include postviral airway inflammation with bronchial hyperresponsiveness, mucus hypersecretion, upper airway cough syndrome (postnasal discharge), or asthma.

TABLE 62-5 Differential Diagnosis of Cough

Acute	Chronic	Chronic: Less Common
Upper respiratory infection: rhinitis, sinusitis, pertussis	Smoking and/or chronic bronchitis	Heart failure
Lower respiratory tract infection: bronchitis, pneumonia	Upper airway cough syndrome (postnasal discharge syndrome)	Bronchiectasis
Allergic reaction	Asthma: reactive airways disease	Lung cancer or other intrathoracic mass
Asthma	Gastroesophageal reflux	Emphysema
Environmental irritants	Angiotensin-converting enzyme inhibitor	Occupational and environmental irritants
Transient airway hyperresponsiveness	Angiotensin II receptor blocker	Recurrent aspiration or chronic foreign body
Foreign body	Postinfectious; pertussis	Psychiatric
		Miscellaneous: cystic fibrosis, interstitial lung disease

CHRONIC COUGH

The most common causes of chronic cough are (1) smoking, often with chronic bronchitis; (2) upper airway cough syndrome (formerly postnasal discharge); (3) asthma; (4) gastroesophageal reflux; and (5) angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) therapy (Table 62-5).[25,26] Smoking-induced coughing is usually worse in the morning and, with chronic bronchitis, usually productive. Upper airway cough syndrome, formerly called *postnasal discharge syndrome*, is associated with mucus drainage from the nose, a history of "allergies or sinus problems," and frequent clearing of the throat or swallowing of mucus.[27] The postnasal drainage itself may not only directly stimulate a cough, but the conditions producing postnasal drainage (e.g., allergic rhinitis) may also cause irritation or inflammation of upper airway structures that directly stimulates cough receptors independently of the drainage. Chronic cough associated with asthma is usually worse at night, exacerbated by irritants, and associated with episodic wheezing and dyspnea.[28] Asthma can be exacerbated by β-blocker therapy and also presents with nocturnal coughing. Cough associated with gastroesophageal reflux often has a history of heartburn, is worse when lying down, and improves with anti-acid therapy (antacids, H_2 blockers, or proton pump blockers).[29]

The incidence of ACE inhibitor cough is approximately 10% to 12%, although higher values have been reported.[30] All ACE inhibitors and ARBs can induce cough, although ARBs appear to have a lower reported incidence.[31] ACE inhibitor cough is thought to result when the blockade of ACE leads to accumulation of bradykinin and substance P, which stimulate the pulmonary cough receptors and enhance the formation of irritating prostaglandin metabolites. ACE inhibitor cough is highly variable in (1) onset (as early as 1 week to as late as 1 year after starting treatment), (2) severity (only slightly bothersome to debilitating symptoms), and (3) variation during the day. Cough typically resolves in 1 to 4 weeks after ACE or ARB therapy is stopped but may linger up to 3 months.[30] See chapter 14, "Anaphylaxis, Allergies, and Angioedema," for further discussion.

DIAGNOSIS AND TREATMENT

Most causes of acute cough do not warrant ancillary tests. A chest radiograph is wise for patients with purulent sputum and/or fever, and spirometry can document the presence of airflow obstruction in patients with asthma. Pertussis is a clinical diagnosis in patients with subacute cough as the commonly available culture, and polymerase chain reaction tests have decreasing sensitivity after the third week of coughing.[14]

ACUTE COUGH

In addition to disease-specific therapy,[32] patients with acute cough may benefit from antitussives, which block the cough reflex at various locations.[33,34] Demulcents, part of most proprietary cough preparations, soothe the pharynx and somewhat suppress the cough reflex. Of the herbal agents, menthol and the pungent spices (e.g., pepper, mustard, garlic, radish, and onions) have an antitussive effect.[35] Naproxen reduces coughing in patients with acute bronchitis.[36,37] In both children and adults, acute coughing illnesses can last up to 3 weeks.[38,39] For intractable coughing paroxysms in the ED, some patients respond to 4 mL of 1% or 2% preservative-free lidocaine (40 or 80 milligrams) by nebulization. This will cause transient suppression of the gag reflex due to posterior pharyngeal anesthesia.

SUBACUTE AND CHRONIC COUGH

Determine if the subacute cough is postinfectious—one following a recent respiratory infection. If postinfectious, then assess for transient bronchial hyperresponsiveness, asthma, pertussis, upper airway cough syndrome, pneumonia, or an acute exacerbation of chronic bronchitis. Treatment is then directed at the presumed cause. If subacute cough is not postinfectious, it is evaluated and treated in the same manner as a chronic cough.

Chronic cough is most often the result of a few common disorders, so an algorithmic approach to treatment using sequential steps is effective[25,26,40] (**Figure 62-5**):

- Reduce exposure to lung irritants (e.g., smoking) and discontinue ACE inhibitors, ARBs, and β-blockers.

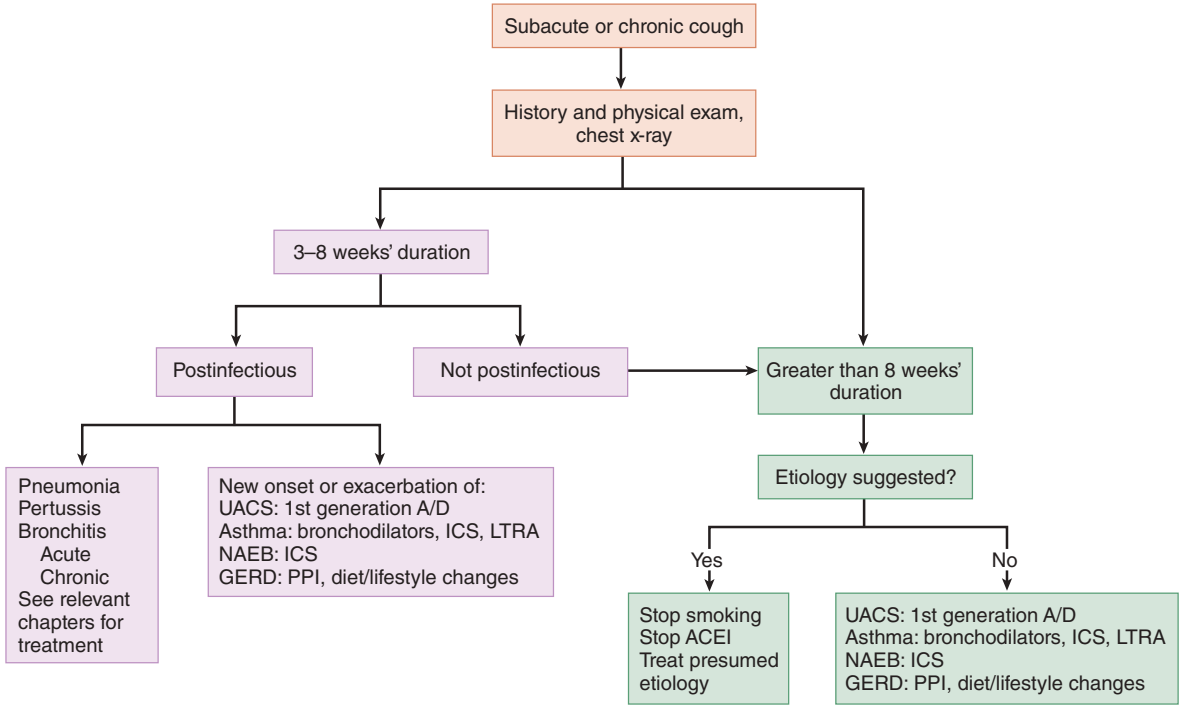


FIGURE 62-5. Evaluation of subacute and chronic cough for patients 15 years of age and older.[23] ACEI = angiotensin-converting enzyme inhibitor; A/D = antihistamine/decongestant; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroids; LTRA = leukotriene receptor antagonist; NAEB = nonasthmatic eosinophilic bronchitis; PPI = proton pump inhibitor; UACS = upper airway cough syndrome.

- Treat for postnasal discharge with an oral first-generation antihistamine/decongestant with or without an inhaled nasal steroid. If the cough improves, continue treatment and evaluate for sinus disease with imaging studies.
- Evaluate and treat for asthma.
- Obtain chest and sinus imaging if not already done.
- Evaluate and treat for gastroesophageal reflux.
- Refer the patient for specialist evaluation, for CT of the chest and evaluation for pulmonary and nonpulmonary causes of cough, or bronchoscopy.

By using a sequential approach, >95% of patients achieve resolution of their cough.[40] Opioid and nonopioid antitussives may help some patients who remain symptomatic.[41]

HICCUPS

Hiccup, or singultus, is involuntary spastic contraction of the inspiratory muscles. Hiccups have no specific protective purpose.[42]

PATHOPHYSIOLOGY

The afferent arm of the hiccup reflex consists of the phrenic and vagus nerves as well as the thoracic sympathetic chain. Normally, glottis closure inhibits inspiration and prevents aspiration during swallowing. Conversely, inspiration normally inhibits glottic closure and maintains an open airway. The hiccup reflex disrupts the connection between these two processes so that 30 to 40 milliseconds after the onset of inspiration, glottic closure is stimulated. In most cases in which a specific cause can be assigned, hiccups appear to result from stimulation, inflammation, or injury to one of the nerves of the reflex arc.

CLINICAL FEATURES

Hiccups are classified as benign and self-limited or persistent and intractable (**Table 62-6**).[42]

Benign hiccups are generally initiated by gastric distention from food, drinking (especially carbonated beverages), or air. Alcohol ingestion appears to precipitate hiccups by relaxing the relationship between inspiration and glottic closure, making it easier for other stimuli to trigger the reflex.

Persistent hiccups are usually a result of injury or irritation to a branch of the vagus or phrenic nerves. One rare but readily treatable stimulus is a foreign body (often a hair) in the external auditory canal that is pressing against the tympanic membrane and stimulating the auricular branch of the vagus nerve. Several drugs—usually steroids and benzodiazepines—are implicated in inducing hiccups, but the evidence is weak.[43]

DIAGNOSIS AND TREATMENT

Determine whether a specific triggering event exists (Table 62-6). Ask if the hiccups persist during sleep; resolution during sleep suggests a psychogenic cause, although this distinction is not absolute. Look in the external auditory canal for a foreign body. A chest radiograph should be done to evaluate for intrathoracic pathology. Fluoroscopy can evaluate for unilateral versus bilateral diaphragmatic movement during hiccups but is not part of the ED evaluation. Unilateral movement suggests focal injury to the phrenic nerve on the affected side.

TABLE 62-6 Differential Diagnosis of Consequence: Hiccups

Acute: Benign, Self-Limited	Chronic: Persistent, Intractable
Gastric distention	CNS structural lesions
Alcohol intoxication	Vagal or phrenic nerve irritation
Excessive smoking	Metabolic: uremia, hyperglycemia
Abrupt change in environmental temperature	General anesthesia
Psychogenic	Surgical procedures: thoracic, abdominal, prostate and urinary tract, craniotomy
	Foreign body in ear touching tympanic membrane (especially hair)

TABLE 62-7 Treatment of Hiccups: Physical Maneuvers

Remove foreign body from ear
Swallow a teaspoon of sugar
Sip ice water
Drink water quickly

A variety of physical maneuvers and medications have been used to terminate an acute episode of hiccups (**Tables 62-7 and 62-8**).[44,45]

Many of these physical maneuvers are based on the concept that stimulating the pharynx will block the vagal portion of the reflex arc and abolish the hiccups.[44] No one method appears to be more effective than another. Swallowing a teaspoon of dry granulated sugar is about as effective as others and does not involve the infliction of noxious or painful stimulation.

Drug treatment (Table 62-8) also works by inhibiting the reflex arc.[44] Several agents are described as effective, but mostly only through case reports.[45] Of the recommended drugs, only chlorpromazine has U.S. Food and Drug Administration approval for treatment of intractable hiccups. Chlorpromazine and metoclopramide take effect within 30 minutes. Adverse effects include extrapyramidal symptoms with both agents and hypotension with chlorpromazine. Nifedipine, valproate, baclofen, and gabapentin[46] are second-line outpatient options usually started by the primary care physician.

CYANOSIS

Cyanosis is a bluish color of the skin and mucous membranes resulting from an increased amount of reduced Hb (deoxyhemoglobin) or Hb derivatives. The detection of cyanosis is subjective and is not a sensitive indicator of the state of arterial oxygenation; cyanosis is determined by the absolute amount of deoxygenated Hb in the blood, not the amount of oxygenated Hb. Cyanosis is divided into central or peripheral categories (**Table 62-9**). **Central cyanosis is cyanosis of mucous membranes and tongue due to inadequate pulmonary oxygenation or an abnormal Hb. Peripheral cyanosis is cyanosis of the fingers or extremities from vasoconstriction and diminished peripheral blood flow.** All conditions that cause central cyanosis also result in peripheral cyanosis.

TABLE 62-8 Treatment of Hiccups: Drug Treatment

Drug	Initial Dose	Maintenance Dose
Chlorpromazine	25–50 milligrams IV, repeat in 2–4 h if needed	25–50 milligrams PO three to four times a day
Metoclopramide	10 milligrams IV or IM	10–20 milligrams PO three times a day for 10 d
Haloperidol	2–5 milligrams IM	1–4 milligrams PO three times a day
Nifedipine	10–20 milligrams PO	10–20 milligrams PO three to four times a day
Valproate	15 milligrams/kg PO	15 milligrams/kg PO three times a day
Baclofen	10 milligrams PO	10 milligrams PO three times a day
Gabapentin	100 milligrams	100 milligrams PO three times a day

TABLE 62-9 Differential Diagnosis of Cyanosis

Central Cyanosis	Peripheral Cyanosis
Hypoxemia	Reduced cardiac output
Decreased fraction of inspired oxygen: high altitude	Cold extremities
Hypoventilation	Maldistribution of blood flow: distributive forms of shock
Ventilation–perfusion mismatch	Arterial or venous obstruction
Right-to-left shunt: congenital heart disease, pulmonary arteriovenous fistulas, multiple intrapulmonary shunts	
Abnormal hemoglobin	
Methemoglobinemia: hereditary, acquired	
Sulfhemoglobinemia: acquired	
Carboxyhemoglobinemia	

CLINICAL FEATURES

Cyanosis is usually visible when deoxygenated Hb exceeds 5 grams/dL, but individuals with sensitive vision in ideal circumstances may detect central cyanosis with deoxyhemoglobin concentration as low as 1.5 grams/dL. Various physiologic, anatomic, and physical factors other than the amount of reduced Hb may influence the appearance of cyanosis, making an accurate clinical detection of the degree or even the presence of cyanosis difficult (**Table 62-10**).

The tongue and buccal mucosa are thought to be sensitive sites for observing central cyanosis. Peripheral cyanosis is caused by the slowing of blood flow to an area and an abnormally large extraction of oxygen from normally saturated arterial blood. Peripheral vascular disease, shock states, heart failure, and cold exposure all create states of vasoconstriction and decreased peripheral blood flow, with cyanosis of the nail beds. Massage or gentle warming of a cyanotic extremity will increase peripheral blood flow and abolish peripheral, but not central, cyanosis.

Pseudocyanosis is a bluish or slate-gray skin discoloration due to drugs (chlorpromazine, minocycline, amiodarone, nicorandil) or heavy metals (gold, silver).[47,48] In pseudocyanosis, the lips and mucous membranes are of normal color, the abnormal skin discoloration does not blanch with pressure, and the discoloration tends to be more intense in sun-exposed areas. Focal areas of pseudocyanosis may be due to local contact with color dyes, gold, or silver.

DIAGNOSIS AND TREATMENT

Pulse oximetry can detect hypoxemia and provide an accurate oxygen saturation measurement. However, with hemoglobinopathy, standard pulse oximetry is often inaccurate. In methemoglobinemia, pulse oximetry will read 80% to 85% regardless of the oxygen level, thereby often overestimating the true oxygen saturation (it may be lower, but pulse oximetry will not read lower). **With carboxyhemoglobinemia, the pulse oximetry reads carboxyhemoglobin as oxyhemoglobin** reporting a higher percentage for oxygen saturation (see chapters 207, "Dyshemoglobinemias," and 222, "Carbon Monoxide"). **Arterial blood gas analysis using co-oximetry (a specific multi-wavelength measurement of oxygen saturation) is needed in the assessment of any patient with suspected cyanosis.** In central cyanosis, the oxygen saturation measured from the arterial blood gas is decreased because of the underlying hypoxemia. In peripheral cyanosis, the oxygen saturation should be normal. With methemoglobinemia or carboxyhemoglobinemia, arterial blood gas co-oximetry will show a normal Pao_2 (reflecting a normal amount of dissolved oxygen in the plasma), a normal calculated oxygen saturation (from the normal Pao_2), and a decreased measured oxygen saturation (because of a decreased number of oxygen-binding sites).

Give oxygen to all patients with central cyanosis; failure to improve suggests impaired circulation (shock), abnormal Hb, or pseudocyanosis.

TABLE 62-10 Factors Influencing the Physical Appearance of Cyanosis

Physiologic factors
Oxygen content of blood
Degree of oxygen extraction
Oxyhemoglobin dissociation curve
Anatomic factors
Status of microcirculation
Skin pigmentation
Skin thickness
Physical factors
Quality/intensity of light in examination area
Skill of examining physician

PLEURAL EFFUSION

Pleural effusions result from fluid accumulating in the potential space between the visceral and parietal pleurae. Although pleural effusions can result from many causes, in developed countries, the most common causes are heart failure, pneumonia, and cancer (**Table 62-11**).[49-51]

PATHOPHYSIOLOGY

A continuous amount of fluid is secreted from the parietal pleura into the pleural space where it is absorbed by the visceral pleural microcirculation, averaging about 8 L/d in an adult. This fluid reduces friction between the pleural layers and allows for smooth lung expansion and contraction with respiration. Any process that increases fluid production or interferes with fluid absorption will result in accumulation in the pleural space. Pleural effusions are traditionally divided into exudates or transudates.[49-51] Exudative effusions result from pleural disease, usually inflammation or neoplasia that produces active fluid secretion or leakage with high protein content. Transudative effusions result from an imbalance between hydrostatic and oncotic pressures. This imbalance results in the production of an ultrafiltrate with low protein content into the pleural space.

CLINICAL FEATURES

A pleural effusion may be clinically silent or come to detection from either symptoms of an underlying disease, an increase in volume of the effusion with the production of dyspnea, or the development of inflammation and associated pain with respiration. Physical findings of a pleural effusion include percussion dullness and decreased breath sounds. Because pleural fluid typically pools in the dependent portions of the hemithorax, small or

TABLE 62-11 Differential Diagnosis of Pleural Effusion

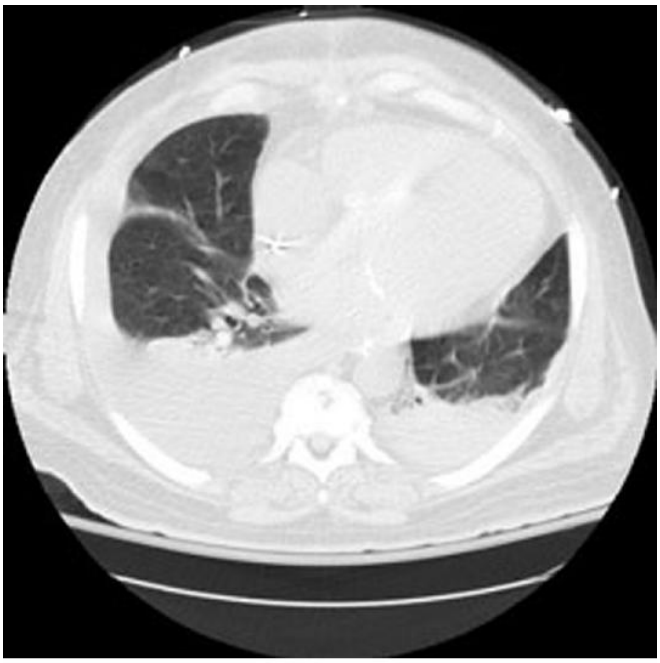
Common	Less Common
Transudates	
Heart failure	Cirrhosis with ascites
	Peritoneal dialysis
	Nephrotic syndrome
Exudates	
Cancer: primary or metastatic	Viral, fungal, mycobacterial, or parasitic infection
Bacterial pneumonia with parapneumonic effusion	Systemic rheumatologic disorders: systemic lupus erythematosus, rheumatoid arthritis
Pulmonary embolism	Uremia, pancreatitis
	Postcardiac surgery or radiotherapy
	Drug-related: amiodarone
Either transudates or exudates	
Transudates after diuretic therapy	Pulmonary embolism

moderate-size effusions have percussion dullness and decreased breath sounds at the lung base with relatively normal lung findings above the level of fluid. With large or massive effusions, it may be impossible to distinguish a fluid level on clinical examination.

DIAGNOSIS

In an adult, 150 to 200 mL of pleural fluid in the hemithorax is required to be detectable on upright chest radiography. Supine chest radiographs may demonstrate only a hazy appearance of pleural fluid in the posterior pleural space (**Figure 62-6A**). CT scanning of the chest may clarify uncertain findings on chest radiograph (**Figure 62-6B**). Small free-flowing pleural effusions are better visualized on decubitus radiographic views (**Figure 62-7**). US can also identify a pleural effusion (Figure 62-3). **A significant pleural effusion is large enough to produce a pleural fluid strip >10 mm wide on lateral decubitus radiographic views or by ultrasonography.**[49]

A



B

FIGURE 62-6. **A**. Supine radiograph showing a right-sided pleural effusion. The right lung field is hazy compared to the left, and a small layer of fluid is noted inferiorly. **B**. CT scan of the same patient. A moderate pleural effusion is seen in the right lung field, and a small effusion not seen in the left lung field of the plain radiograph is present on the CT scan.

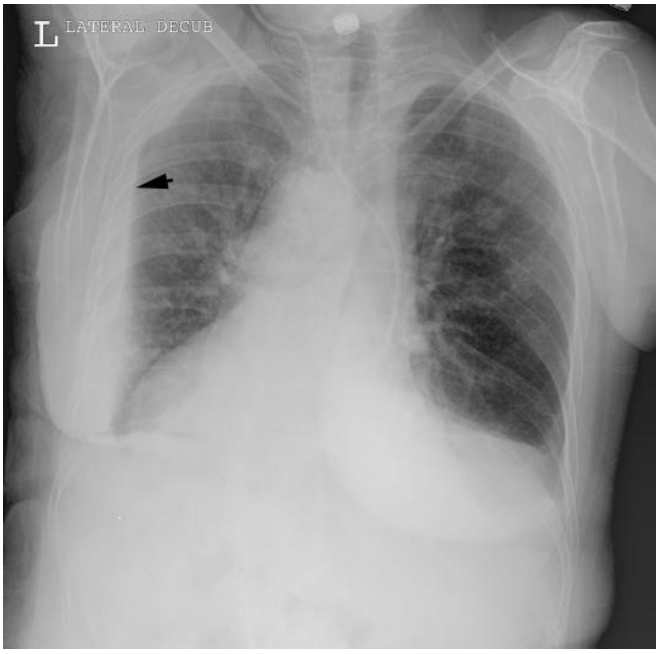


FIGURE 62-7. Left lateral decubitus radiograph showing a layering of a small pleural effusion. *Arrowhead* points to the layer of fluid.

Diagnostic thoracentesis is done to obtain pleural fluid for analysis in cases without a clearly evident cause, to confirm a suspected diagnosis, or to detect pleural space infection. For example, because the largest single cause of pleural effusion is heart failure, if a patient presents with a typical appearance (cardiomegaly, roughly equal in size bilateral effusions), then a period of treatment with monitoring for pleural fluid resolution is indicated, and routine thoracentesis is reserved for patients who do not experience resolution in 3 to 4 days. Otherwise, diagnostic thoracentesis and pleural fluid analysis are indicated.

Light developed the most widely used criteria to differentiate transudates from exudates using serum and pleural fluid protein and lactate dehydrogenase levels (**Table 62-12**).[52] Modifications to the original criteria have been proposed,[51,53] but the overall sensitivity for the detection of an exudative pleural effusion remains 98% to 99% with specificity from 65% to 86%. If the clinical circumstances suggest that the effusion is likely to be transudative, the only tests indicated are pleural fluid and serum protein content and lactate dehydrogenase levels. If the pleural effusion is exudative, additional tests are indicated (Table 62-12).[49-51]

The distinction between exudates and transudates may be obscured by the effect of diuretic therapy in patients with transudative pleural effusions.[49,50] During diuresis, the resorption of water is faster than that of protein, so the protein concentration rises into the range consistent with an exudative etiology. A serum to pleural albumin difference of >1.2 grams/dL has been proposed to help in this scenario, but this approach will reduce the sensitivity of exudative pleural effusion detection by >10%.[49,50,52]

TREATMENT

Therapeutic thoracentesis with drainage of 1.0 to 1.5 L of fluid is indicated if the patient has dyspnea at rest. Acute drainage of larger volumes is associated with reexpansion pulmonary edema, so large-volume