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Concepts and Clinical Practice

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Chronic Obstructive Pulmonary Disease

Patricia Ruth Atchinson and Matthew A. Roginski

KEY CONCEPTS

- Chronic obstructive pulmonary disease (COPD) is "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."
- COPD exacerbation is a worsening of symptoms from baseline beyond day-to-day variation and requiring additional treatment. It is most commonly caused by viral infections, bacterial infections, environmental pollutants, particulate matter, thrombotic disease, or temperature changes.
- Dyspnea, cough, increased sputum production, and sputum purulence are the most common symptoms of COPD exacerbations. They are a result of airway inflammation, increased mucus production, and air trapping.
- Treatment includes nebulized short-acting beta-agonists such as albuterol, short-acting anticholinergics such as ipratropium, and glucocorticoids such as prednisone.
- Antibiotics should be given to patients with COPD exacerbations who have signs of lower respiratory tract infection, increased purulence of their sputum, or who have respiratory failure. Antibiotics should be provided empirically based on local resistance patterns to *Streptococcus pneumoniae, Moraxella catarrhalis,* and *Haemophilus influenzae* with common regimens including amoxicillin/clavulanate, macrolides, or tetracyclines.
- Patients with COPD are at increased risk for thromboembolic disease due to a sedentary lifestyle and chronic inflammation. Patients admitted for COPD exacerbation presenting a pleuritic chest pain or signs of heart failure without an infectious precipitant should be screened for pulmonary embolism.
- Patients with COPD exacerbations commonly present with tachyarrhythmias including atrial fibrillation, atrial flutter, and multifocal atrial tachycardia.
- Oxygen supplementation should be administered with a saturation goal of 88% to 92%.
- In severe exacerbations, patients develop a rapid, shallow breathing pattern which decreases the exhalation time, causes hyperinflation, increases the proportion of dead space ventilation, and causes respiratory muscle fatigue.
- Bi-level noninvasive ventilation is the first-line therapy for patients with hypercapnic respiratory failure and acute COPD exacerbations without hemodynamic instability, severe agitation, or respiratory arrest. Implementing noninvasive ventilation decreases the mortality, intubation rates, and hospital length of stay.
- If intubation is required, ventilation priorities are decreasing the patient work of breathing and limiting dynamic hyperinflation primarily using a low respiratory rate of 10 to 14 breaths/min and tidal volume of ≤8 mL/kg predicted by body weight. Respiratory acidosis with a pH greater than 7.2 should be tolerated without manipulating the minute ventilation.
- All patients being discharged from the emergency department should be counseled on smoking cessation, adequate inhaler techniques, and offered pneumococcal and influenza vaccination if not current.

FOUNDATIONS

Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in the United States and worldwide[1] with a high financial burden to the healthcare system and frequent presentation to the emergency department (ED). The prevalence of COPD is likely underrecognized.[2,3] A large multinational collaboration called the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was created to develop guidelines worldwide to improve prevention and treatment of COPD. GOLD defines COPD as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[1] COPD is caused by both environmental and genetic factors. Cigarette smoking is the most important risk factor for developing COPD, but fewer than half of smokers will develop COPD. Other risk factors include an age greater than 40 years, male gender, occupational exposures, indoor air pollution, and genetic factors such as alpha-1 antitrypsin deficiency.

Airflow limitation diagnosed by spirometry determines the disease severity. Symptom burden and exacerbation risk are also incorporated into the diagnostic criteria. Treatment recommendations of the stable patient incorporate both the airflow obstruction and symptom burden. Patients with COPD have a high prevalence of concomitant comorbid conditions, including ischemic heart disease, atrial fibrillation, heart failure, metabolic syndrome, musculoskeletal disease, anxiety, depression, and lung cancer.[4]

Anatomy/Physiology/Pathophysiology

The tracheobronchial tree is composed of large conducting airways that divide into smaller bronchi and bronchioles terminating in a functional lung unit called a pulmonary acinus. The acinus is supplied by a first order respiratory bronchiole and includes alveolar ducts and alveolar sacs (Fig. 60.1). The larger bronchi are in close proximity to pulmonary arteries and lymphatics and not directly connected to the lung parenchyma. They remain patent because of their cartilaginous structure and the pressure gradient from the alveolar to the intrathoracic space. Smaller bronchioles (<1 to 2 mm) are embedded in lung parenchyma and do not have a cartilaginous structure; they remain patent because of the elastic recoil of the lung parenchyma. Collectively, the total cross-sectional area of the bronchioles is approximately 100 times greater than that of the large proximal airways and, under normal circumstances, do not contribute to flow resistance. In COPD, progressive changes within the bronchial tree and the lung parenchyma cause airflow resistance.

Frequent exposure to noxious stimuli (e.g., cigarette smoke or small particles) induces inflammation in the airways and pulmonary parenchyma. Lymphocytes, macrophages, and neutrophils infiltrate inflamed tissues. Over time, a chronic inflammatory response leads

to remodeling and destruction of the normal tissue by oxidative stress and protease activity. Inflammation in the bronchi and bronchioles results in increased mucus production with submucosal gland enlargement and goblet cell metaplasia, decreased mucociliary clearance, and increased permeability of the airspace epithelial border. Sustained inflammation can result in the remodeling of smooth muscle and connective tissue, epithelial hypertrophy, and fixed obstruction in small airways from fibrosis.

Inflammation in the lung parenchyma destroys the connective tissue matrix of alveolar walls and septae. The balance of protease/antiprotease activity has an essential role in disease progression. Activated neutrophils are the primary producer of elastase in the lungs, and neutrophil elastase destroys the matrix of lung parenchyma. The action of neutrophil elastase is inhibited by alpha 1-antitrypsin. Patients who are deficient in alpha 1-antitrypsin, as well as patients who are chronically exposed to noxious stimuli, leading to the activation of neutrophils in the pulmonary parenchyma, have significant parenchymal damage.

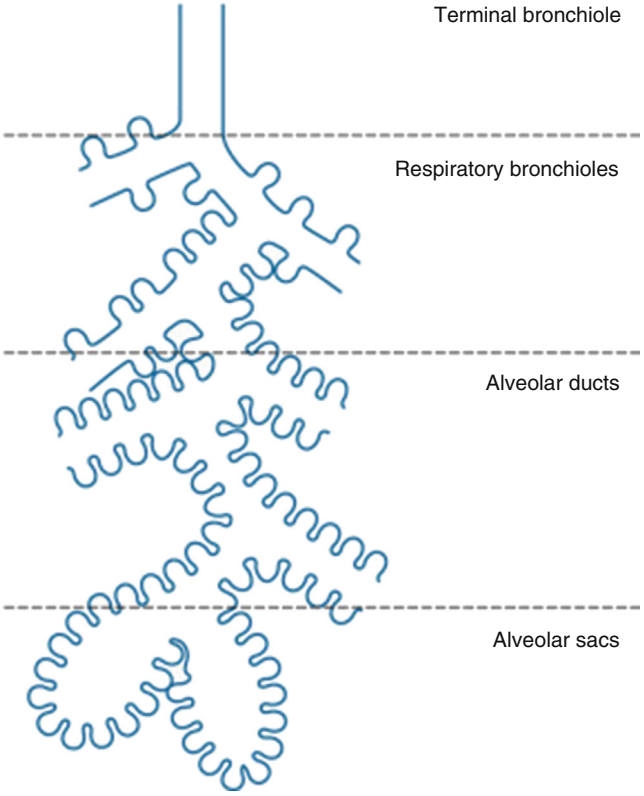

Fig. 60.1 Diagram of a single pulmonary acinus displaying the generations between terminal bronchiole and alveolar sacs. (From Nunn's Applied Respiratory Physiology. Lumb, Andrew B, MB BS FRCA. Published January 1, 2017. Pages 3–16.e1. © 2017. Figure 1.6.)

COPD is a multifactorial and heterogeneous disease with different aspects of the disease progressing independently of the another. Patients are no longer categorized as having primarily emphysematous or chronic bronchitis phenotypes because both often coexist. Emphysema is a pathological diagnosis referring to the destruction of the lung parenchyma. Pulmonary parenchymal destruction results in gas trapping and airflow obstruction. The pattern and location of damage can vary based on precipitating factors. Patients with alpha 1-antitrypsin deficiency usually have panacinar emphysema predominantly in the lower lung zones, whereas chronic smokers typically have central acinar emphysema predominantly in the upper lung zones (Fig. 60.2). Severity of airflow obstruction and air trapping are proportional to the amount of parenchymal destruction. Decreased and damaged lung parenchyma provide less traction on the small bronchioles (<1 to 2 mm) embedded in the parenchyma and requiring an intact architecture for patency. As airflow obstruction and parenchymal destruction worsen, the total number of terminal bronchioles is also reduced.[5] This combination of events leads to decreased gas exchange, decreased pressure gradient from the alveoli to the conducting airways during exhalation, and collapse of the bronchioles leading to gas trapping (Fig. 60.3). Fig. 60.4 shows evidence of parenchymal destruction in a patient with COPD and emphysema on contrast enhanced chest CT.

Chronic bronchitis is diagnosed in the presence of cough and sputum production for most days over 3 months for at least 2 consecutive years. These patients have increased mucus production, decreased ciliary clearance and chronic bronchial inflammation. They are likely to have central hypoxemia because of these changes. There are efforts to clarify different endotypes of COPD to develop targeted treatments. For example, alpha 1-antitrypsin deficiency and inflammation that has an eosinophilic predominance may be more amenable to steroids.[4] Asthma-COPD overlap syndrome has clinical features of both asthma and COPD regarding bronchial hyperresponsiveness and etiology of inflammation.[6] Differentiation is of limited clinical utility in the ED.

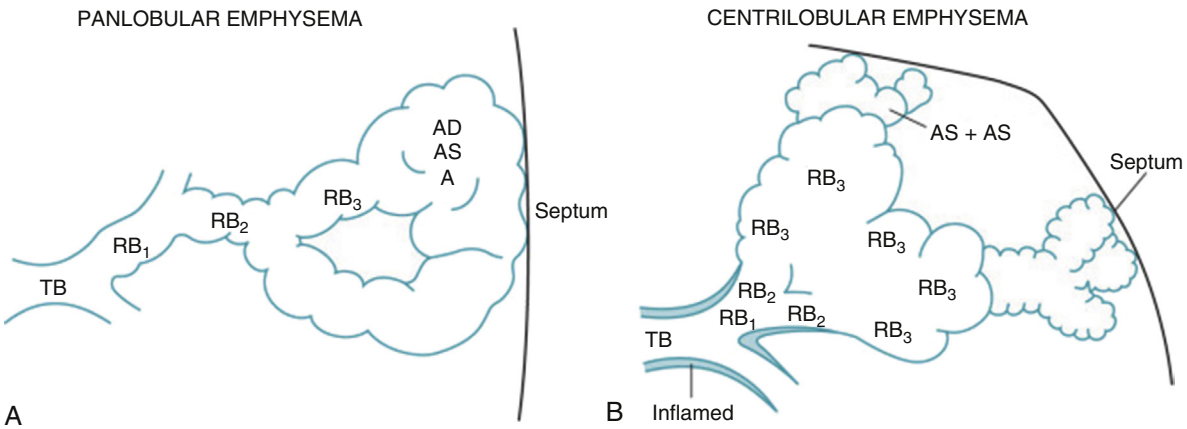

Fig. 60.2 Diagram of panacinar (A) and centriacinar (B) emphysema. Panacinar emphysema (A) has uniform enlargement of the acinus. Centriacinar emphysema the enlargement is primarily at the level of the respiratory bronchiole and not alveolar sacs. *A*, Alveolus; *AD*, alveolar duct; *AS*, alveolar sac; *RB 1, 2, 3*, three generations of respiratory bronchioles; *TB*, terminal bronchiole. (From Thurlbeck WM. Chronic obstructive lung disease. In: Sommers SC, ed. *Pathology Annual*, vol 3. New York, NY: Appleton-Century-Crofts; 1968.)

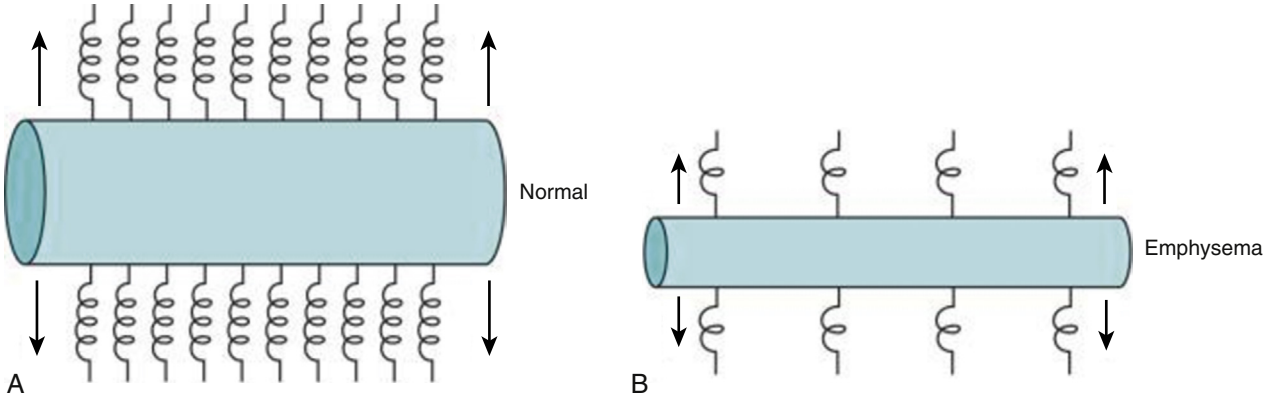

Fig. 60.3 Schematic diagram of traction exerted by alveolar walls (shown by springs), acting to keep the airways open. (A) Normal. (B) Loss of traction seen in emphysema. (From Weinberger, Steven E., MD, MACP, FRCP; Cockrill, Barbara A., MD; Mandel, Jess, MD, FACP. Published December 31, 2018. Pages 93–112. Copyright © 2019 by Elsevier, Inc.)

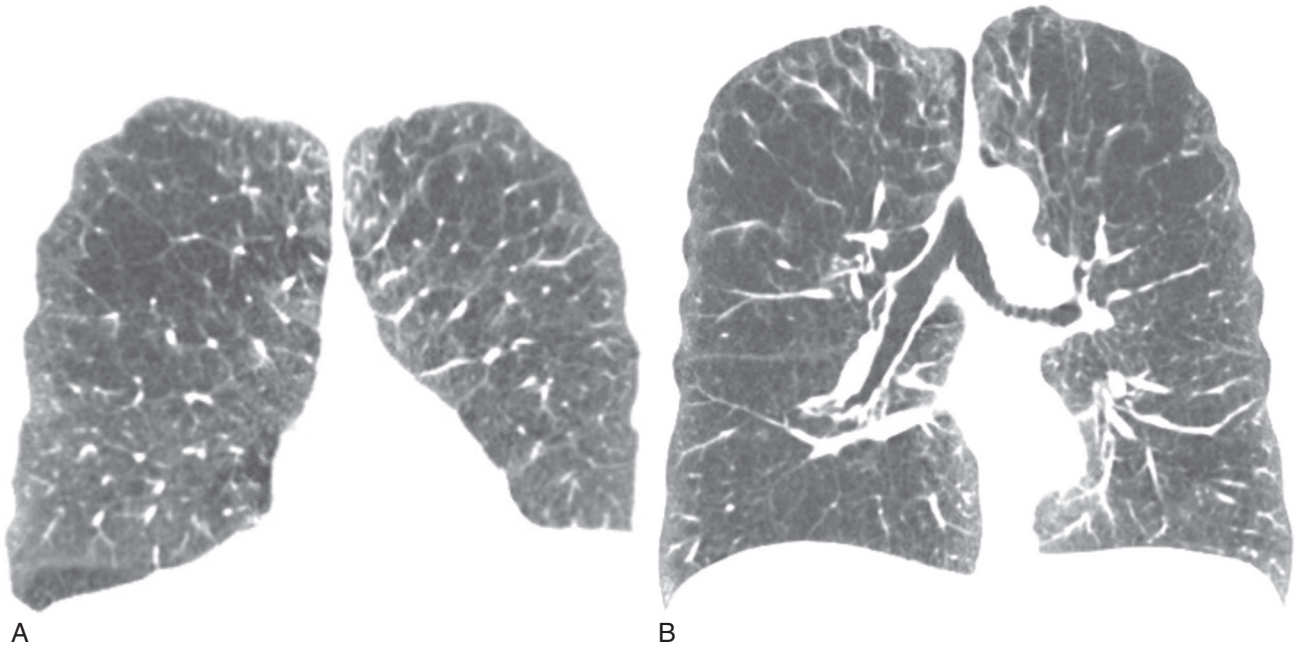

Fig. 60.4 (A and B) Coronal contrast enhanced CT images in a patient with emphysematous chronic obstructive pulmonary disease. Decreased attenuation in the right and left upper lung zones represents the parenchymal destruction and loss.

Pulmonary hypertension may be present in patients with severe COPD because of changes in the pulmonary vasculature and surrounding structures. Late in the course of COPD, there is often chronic hypoxia secondary to lung parenchyma destruction. Hypoxic vasoconstriction in the small vessels of the pulmonary arterial bed and loss of pulmonary capillaries result in vascular remodeling, intimal hyperplasia, smooth muscle hyperplasia, and hypertrophy. Hypoxic vasoconstriction may be reversible, but vascular remodeling may not be. As the disease progresses, pulmonary hypertension (cor pulmonale), and right ventricular remodeling may result. These progressive changes are also associated with a patient's clinical course. For example, a large pulmonary artery to aorta ratio on CT scan is associated with an increased risk of COPD exacerbation.

As airflow obstruction and increasing air trapping develop on the microscopic pulmonary acinus level, there are associated changes in the macroscopic lung physiology. COPD patients have increased residual volume, functional residual capacity (FRC), and total lung capacity due to hyperinflation. This contributes to the increase in dead space and decline of forced expiratory volume in one second (FEV_1) because of the loss of lung tissue and loss of elastic recoil of the lungs. Over time these changes cause the diaphragm to flatten with a decreased zone of opposition causing a decrease in mechanical efficiency. The rib cage also changes with an increase in the antero-posterior diameter (Fig. 60.5). These changes are associated with decreased respiratory efficiency and increased energy consumption to maintain an adequate minute ventilation. Patients with these underlying changes have a decreased respiratory reserve in the setting of a COPD exacerbation, pneumonia, or metabolic acidosis that requires respiratory compensation.

Clinical Features

The diagnosis of COPD should be considered in patients who have progressive dyspnea, chronic cough or sputum production, recurrent

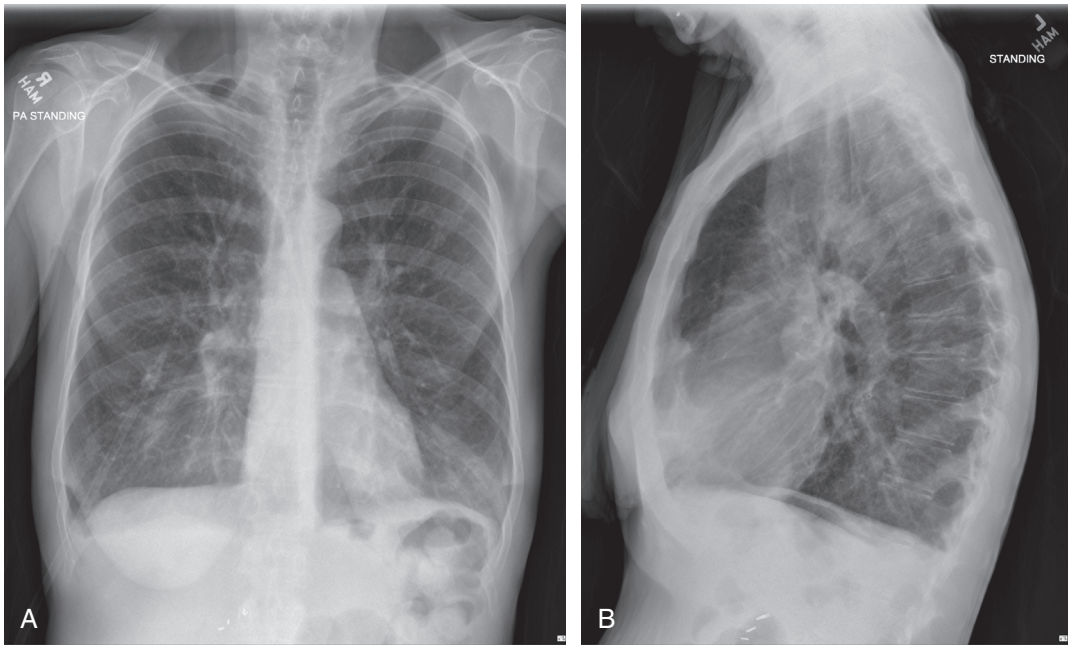

Fig. 60.5 (A and B) Chest x-rays displaying typical changes seen in chronic obstructive pulmonary disease. A is a posterior-anterior chest x-ray showing hyperinflated lungs and a flattened diaphragm. B is a lateral chest x-ray showing hyperinflated lungs and a flattened diaphragm and with an increased antero-posterior diameter.

lower respiratory tract infections or have multiple risk factors.[1] The diagnosis of COPD requires spirometry-proven airflow limitation defined as the ratio of FEV_1 divided by forced vital capacity (FVC) after bronchodilators of less than 0.7. Patients who have normal spirometry with chronic symptoms and possible emphysema on CT scan are not considered to have COPD.[7] Airflow limitation may worsen over time, especially in the setting of continued exposure to noxious stimuli, and is frequently associated with escalating patterns of worsening exacerbations. However, it is difficult to predict the progression of airflow limitation for an individual, because a small subset of patients get stable or improve over time.[8,9]

The GOLD classification of COPD incorporates the severity of spirometric abnormalities, nature and magnitude of the symptoms, history of moderate to severe exacerbations, and comorbid conditions because the health status and spirometric abnormalities have a weak correlation. The severity of COPD is graded by the degree of airflow obstruction (FEV_1) after bronchodilation (Table 60.1). In addition to the grade, the "ABCD" assessment tool incorporates symptomatic assessment and risk of exacerbations to better assess patients and guide therapy. The letter group is determined by the Modified British Medical Research Council (mMRC) Questionnaire[10] or COPD Assessment Test (CAT)[11] as well as the exacerbation history (Table 60.2). While emergency physicians are not tasked with diagnosing COPD, understanding the spirometric and letter grading provides a more complete understanding of the disease severity, symptom burden, medication regimen, and risk for hospitalization and decompensation.

Acute Exacerbations

A COPD exacerbation is an acute worsening of respiratory symptoms from baseline day-to-day variations that require additional therapy.[1,12] Exacerbations can be triggered by respiratory infection, environmental pollutants, particulate matter, thrombotic disease, or temperature changes. Respiratory infections are more commonly viral, with bacterial infections implicated in 30% to 50% of exacerbations. The most commonly implicated bacterial causes include *Haemophilus influenzae,*

TABLE 60.1 Severity Classification of Airflow Limitation in Patients With COPD (FEV_1/FVC <0.7)

GOLD Classification of Airflow Limitation Severity in COPD (based on post-bronchodilator FEV_1)		
GOLD 1	Mild	FEV_1 ≥80% predicted
GOLD 2	Moderate	50% ≤FEV_1 <80% predicted
GOLD 3	Severe	30% ≤FEV_1 <50% predicted
GOLD 4	Very Severe	FEV_1 <30% predicted

COPD, Chronic obstructive pulmonary disease; *FEV_1*, forced expiratory volume in one second; *FVC*, forced vital capacity; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease.
Adapted from GOLD 2020 guidelines. Gold Reports for Personal Use. *Global Initiative for Chronic Obstructive Lung Disease—GOLD*. https://goldcopd.org/gold-reports/. Accessed January 17, 2020.

TABLE 60.2 GOLD ABCD Assessment Tool

Moderate to Severe Exacerbation History	≥2 or ≥1 leading to hospital admission	C	D
	0 or 1 (not leading to hospital admission)	A	B
		Mild (mMRC or CAT)	Severe (mMRC or CAT)
		Symptoms burden	

The letter provides information about symptom burden and risk of exacerbation in addition to the airflow limitation severity classification that can be used to guide future therapy.
Adapted from GOLD 2020 guidelines. Gold Reports for Personal Use. *Global Initiative for Chronic Obstructive Lung Disease—GOLD*. https://goldcopd.org/gold-reports/. Accessed January 17, 2020. *CAT*, COPD Assessment TEST. This is an 8-item measure of health status impairment in COPD. *mMRC*, Modified British Medical Research Council Questionnaire.

Streptococcus pneumoniae, and *Moraxella catarrhalis*. The most commonly isolated virus is rhinovirus, and viral infections may have a longer and more severe course. Patients presenting with a COPD exacerbation without a clear exposure or infectious risk should be screened for pulmonary embolism, especially if pleuritic chest pain or signs of heart failure are present.[13,14]

Exacerbations are considered mild when only worsening of symptoms are reported, moderate when the patient receives antibiotics or systemic glucocorticoids, and severe when the patient requires an ED visit.[1,4,15] Exacerbations are commonly associated with dyspnea, cough, increased sputum production, and sputum purulence. Depending on the severity, dyspnea and respiratory symptoms may occur at rest or with exertion. Coughing spells may be associated with chest pain from irritation of the intercostal muscles or atraumatic rib fractures in severe cases. Severe coughing episodes may precipitate syncope because of the increase in intrathoracic pressure and decrease in cardiac preload. Inflammation and mucous production increase air trapping, combined with chronic changes to pulmonary mechanics and impaired ability to compensate; this ultimately leads to decreased respiratory efficiency, increased dead space ventilation, and dynamic hyperinflation. As the work of breathing increases, the proportion of cardiac output required by the respiratory musculature increases, further limiting the patient's ability to compensate, and predisposing the patient to progressive respiratory failure.

Respiratory Failure

Patients with a declining respiratory status have a breathing pattern marked by small, frequent breaths through pursed lips. This change in breathing pattern decreases the exhalation time, increases the proportion of dead space ventilation, and has a high energy cost. Many of these patients experience expiratory flow limitation (EFL), in which expiratory flow does not increase despite an increase in the gradient from alveolar pressure to ambient air pressure.[16] In patients with EFL, exhalation to passive FRC (complete exhalation) depends on the expiratory time and not the patient effort. Increased patient effort and pleural pressure do not result in faster expiratory airflow. EFL predisposes patients to dynamic hyperinflation and alveolar overdistension with tachypnea.

Dynamic hyperinflation occurs when inhalation occurs prior to complete exhalation because of truncated expiratory time. Dynamic hyperinflation increases the end-expiratory lung volume, with alveolar overdistension, increased intrathoracic pressure, and decreased lung compliance. These factors subsequently result in an elevated work of breathing, increased dead space ventilation, respiratory muscle fatigue, and hypercapnia culminating in respiratory failure. Clinical definitions of respiratory failure consider respiratory rate, accessory muscle use, increases in the arterial partial pressure of carbon dioxide ($PaCO_2$), and hypoxemia. Definitions of respiratory failure are displayed in Box 60.1.

Differential Diagnosis for the Emergency Presentation

The differential diagnosis for a COPD exacerbation, displayed in Box 60.2, includes pulmonary, cardiac, and metabolic conditions. Respiratory decompensation may be from pneumonia, bleb rupture and pneumothorax, or pleural fluid collection. Pulmonary embolism should be considered in patients without an infectious prodrome, unexplained pleuritic chest pain, signs of new heart failure, or in those whose vital sign abnormalities are out of proportion to the clinical exam. Traumatic or pathologic rib fractures from coughing can cause chest pain and dyspnea. Chest pain may also be related to hyperinflation and overdistention of the respiratory muscles causing discomfort. Patients with COPD have increased risk of coronary artery disease, arrhythmias, and heart failure. Acute cardiogenic pulmonary edema may also present as dyspnea and wheezing. Progressing pitting edema may represent cor pulmonale. Patients at risk for lung cancer may present with dyspnea in the setting of malignant pulmonary or pericardial effusions. Metabolic acidosis or sepsis may present as dyspnea and tachypnea because changes in the respiratory system in severe COPD limit respiratory compensation of a metabolic process.

BOX 60.1 Classification of Respiratory Failure in COPD Exacerbation

No respiratory failure
- Mild tachypnea with rate of 20–30 breaths per minute
- Normal work of breathing
- Baseline mental status
- Mild hypoxemia responsive to oxygen by nasal cannula
- No hypercapnia

Acute respiratory failure
- Significant tachypnea with rate >30 breaths per minute
- Increased work of breathing with accessory muscle use
- Baseline mental status
- Hypoxemia responsive to supplementation with <35% FiO_2
- Hypercapnia with $PaCO_2$ 50–60 mmHg and pH >7.25

Severe respiratory failure
- Altered mental status
- Hypoxemia requiring supplementation with >35% FiO_2
- $PaCO_2$ >60 mm Hg or pH ≤7.25

BOX 60.2 Differential Diagnosis of an Acute Chronic Obstructive Pulmonary Disease Exacerbation

Differential Diagnosis for COPD and COPD Exacerbation

Pneumonia
Pneumothorax
Pleural effusion
Pulmonary embolism
Pulmonary edema
Cardiac arrhythmia
Malignancy
Pericardial effusion
Heart failure
Metabolic acidosis with compensatory tachypnea

COPD, Chronic obstructive pulmonary disease.

Diagnostic Testing

In the outpatient setting, the diagnosis of COPD relies upon spirometry. Patients with symptoms and risk factors suggestive of COPD should be referred for formal evaluation. The diagnosis of COPD exacerbation is clinical and based on a worsening of the patient's baseline symptoms including increased dyspnea, changes in sputum production or increased sputum purulence, and cough.

Chest Radiography

A chest x-ray should be obtained for patients to evaluate a new alveolar process such as a lobar pneumonia, pneumothorax, pulmonary

edema, lobar atelectasis, effusion, or malignancy. Typical findings in a COPD exacerbation without the aforementioned pathology include hyperinflated lung fields, decreased vascular markings, increased antero-posterior diameter, and flattening of the diaphragms (see Fig. 60.5). Bullae may be present and can mimic pneumothorax on chest x-ray and pulmonary ultrasound. If there is diagnostic uncertainty for bullae versus pneumothorax, a CT scan should be performed given its greater sensitivity.

Pulse Oximetry

Continuous pulse oximetry should be used to identify hypoxemia and titrate oxygen therapy.

Blood Gas Analysis

We recommend an initial blood gas in patients presenting with acute respiratory failure. A venous blood gas provides an accurate determination of both pH and hypercapnia. A normal $PaCO_2$ on a venous blood gas can exclude hypercapnic respiratory failure.[17] If there is severe hypercapnia or hypoxia, correlation with an arterial blood gas is recommended. An arterial or venous $PaCO_2$ is recommended if end-tidal capnography is being used because of a possible $PaCO_2$ to end-tidal CO_2 discrepancy in the setting of an increased dead space fraction.

Electrocardiogram

An electrocardiogram should be performed in all patients presenting with acute dyspnea. Tachycardia and tachyarrhythmias, including atrial fibrillation, atrial flutter, multifocal atrial tachycardia, and ventricular arrhythmias, occur in up to 35% of patients presenting with COPD exacerbations.[17] Patients with COPD are at increased risk for ventricular tachycardia when compared to the general public, independent of their left ventricular ejection fraction.[18,19] Patients with COPD commonly exhibit P pulmonale, large (>2.5 mm) peaked P waves in leads II, III, and aVF, and >1.5 mm in V1 and V2, low QRS voltage (due to hyperinflated lung between the chest wall and the heart), and poor R wave progression (≤3 mm in V3) in the precordium.

Laboratory Tests

The utility of C-reactive protein (CRP) in COPD management is a developing area of research. Some studies describe that a low CRP decreases the prescription of antibiotics in COPD exacerbations without increasing the proportion of treatment failure.[20–22] We do not think there is sufficient evidence at this time to support using CRP to guide antibiotic prescribing.

Procalcitonin (PCT) has also been considered as a screening test to guide the use of antibiotics, with some studies suggesting that a low PCT can safely be used to decrease antibiotic prescriptions in COPD exacerbation.[23] However, in patients admitted to intensive care units, PCT-guided therapy was associated with worse mortality at 3 months, suggesting that in the critically ill, the prompt administration of antibiotics outweighs the need for judicious antibiotic prescribing.[24]

We also recommend a complete blood count to screen for anemia and a metabolic profile to screen for metabolic acidosis or hyperglycemia. A troponin should be obtained if there is concern for myocardial ischemia. A D-dimer should only be obtained to screen for an acute pulmonary embolism after prior appropriate risk stratification.

Management

Short-Acting Beta Agonists

Short-acting beta agonists (SABAs) with or without short-acting anticholinergics are the cornerstone of COPD exacerbation management. SABAs work through relaxing airway smooth muscle by stimulating beta-2 adrenergic receptors, increasing cyclic adenosine monophosphate (AMP) and producing a functional antagonism to bronchoconstriction. Short-acting anticholinergics prevent the bronchoconstrictive effects of acetylcholine on M2 muscarinic receptors expressed by smooth muscles. In an acute exacerbation, data do not support the use of nebulizers over metered dose inhalers to deliver these medications.[25,26] In the emergency setting, we recommend the use of nebulized medications instead of devices that require adequate inspiratory flow, breath holding, muscle coordination, and proper technique to promote adequate medication disbursement.[26,27] We recommend air-driven nebulizers rather than oxygen-driven nebulizers if available.[28] Patients may receive SABAs hourly for 1 to 3 hours then every 2 to 4 hours based on response. Continuous nebulization not indicated.

Glucocorticoids

Glucocorticoids act as potent anti-inflammatory mediators by inhibiting cytokine expression and eosinophils via induction of eosinophil apoptosis. They are recommended in COPD exacerbation because they decrease the recovery time, improve oxygenation, improve lung function, and decrease hospital length of stay. These benefits outweigh the risks, including infection, thromboembolism, osteoporosis, diabetes, and hypertension. Bioavailability is similar between oral and parenteral corticosteroids; thus we recommend oral glucocorticoids for patients able to tolerate oral medications or with enteral access. We recommend 40 mg oral prednisone for 5 days, because 5 day courses are as effective as longer courses.[29] Eosinophilia-guided therapy may be as effective as the standard 5-day course of steroids in patients ≥40 years old and hospitalized for COPD[30] but this is not part of the standard treatment recommendations at this time.

Antibiotics

The role of antibiotics in COPD exacerbation remains controversial. There is no clear mortality benefit of using antibiotics in patients who are to be discharged from the ED without signs of lower respiratory infection on chest imaging. The GOLD collaborators recommend the administration of antibiotics to patients with COPD exacerbation who note increased sputum purulence as well as increased dyspnea or increased sputum volume. Antibiotics should be provided empirically based on local resistance patterns to *S. pneumoniae, M. catarrhalis,* and *H. influenzae* with common regimens including amoxicillin/clavulanate, macrolides, and tetracyclines. Patients with chronic severe airflow limitations, known bronchiectasis, and or those that require mechanical ventilation should receive antibiotic coverage that includes pseudomonas. Data does not suggest a specific duration of treatment with antibiotics in those patients who are discharged from the ED. We recommend a 5-day course of macrolides or a 7-day course of amoxicillin/clavulanate or tetracyclines as initial antibiotic therapy, along with follow up with their primary care physician or pulmonologist within 10 days of discharge with attention to decreased sputum purulence as a marker of improvement. Any patient requiring ventilatory support via either noninvasive ventilation (NIV) or endotracheal intubation should receive antibiotics as there is a clear mortality benefit in these patients.

Adjunctive Treatments

All actively smoking patients who present a COPD exacerbation should be counseled on smoking cessation. Inhaler technique should be assessed, and counseling provided in case of inadequate techniques. Patients should be up to date on influenza and pneumococcal vaccinations unless contraindicated. There is no conclusive role for antitussive therapy. Patients being hospitalized should have vitamin D level checked and supplemented if below 25 nmol/L or above 10 ng/mL.[31]

Methylxanthines are not recommended. Heliox is not recommended as a treatment adjunct.[32–34]

Respiratory Support

Oxygenation

Hypoxemia is a common finding in patients with severe COPD and during a COPD exacerbation. The precipitating factors of hypoxemia are multifactorial, including changes in the ventilation and perfusion ratios because of hyperinflation and bronchospasm, mucous plugging, alveolar infiltration, disproportionate blood flow in under-ventilated areas, and increased oxygen consumption leading to decrease venous oxygen tension. Both hypoxemia and hyperoxemia should be avoided. Supplemental oxygen should be titrated to maintain an arterial partial pressure of oxygen (PaO_2) greater than 60 mm Hg and peripheral oxygen saturation between 88% and 92%. Prolonged exposure to high concentrations of inspired oxygen may result in increasing hypercapnia. The primary mechanism is thought to be from a change in the ventilation and perfusion ratios by altering hypoxic vasoconstriction to under-ventilated lung zones. The hypoxic respiratory drive does not appear to be a major contributor in most hypercapnic patients in respiratory distress, but there does appear to be a subset of patients in whom $PaCO_2$ increases in the setting of hyperoxia. The Haldane effect (high oxygen tension induces right shift in the CO_2 dissociation curve and increases the $PaCO_2$) may also contribute to hypercapnia. Normally, this is compensated for by an increase in minute ventilation, but if the patient cannot increase their minute ventilation, $PaCO_2$ will increase.

Non-Invasive Ventilation

Bi-level NIV is the first-line therapy for patients with an acute COPD exacerbation with respiratory failure (see Table 60.3 for indications and contraindications). NIV decreases the mortality, intubation rates, and hospital length of stay.[1,15,35,36] The inspiratory positive airway pressure (IPAP) of NIV helps offload respiratory muscles and aid in the work necessary to overcome the intrinsic positive end expiratory pressure (iPEEP). Initiating NIV changes the patient's breathing pattern; the respiratory rate decreases, allowing a more effective emptying of the lungs, and the patient can take breaths with larger tidal volumes, improving alveolar ventilation. If possible, a chest x-ray, blood gas, and respiratory assessment are recommended prior to the initiation of NIV to evaluate for pneumothorax, tachypnea, accessory muscle use, pH, and $PaCO_2$.

We recommend initial settings of an IPAP of 12 to 15 cm H_2O and an expiratory positive airway pressure (EPAP) of 5 cm H_2O through a facemask tightened to minimize air leaks. Inspired oxygen should be quickly titrated to an oxygen saturation of 88% to 92%. While fitting the mask on the patient, a nurse, respiratory therapist, or physician should explain the process to the patient because of the associated anxiety during mask placement while in respiratory distress. An adjunctive fan directed at the patient's face or adjunctive low dose morphine may relieve the sensation of breathlessness.[37–39] Should the patient have increased work of breathing on these initial settings, we recommend increasing the IPAP by increments of 2 to 3 cm H_2O every 2 to 3 minutes to a maximum IPAP of 25 cm H_2O. Improvement in pH and respiratory rate predict treatment success and are usually seen in the first 1 to 4 hours after initiation.[40]

Failure of NIV may occur because of the severity of the underlying disease, severity of comorbidities, or inability to tolerate therapy. The overall failure rate is approximately 10% to 15%[41] but increases with a lower presenting pH and severity of illness. In general, patients initiated on NIV should be reassessed for the same indications they were started on NIV (tachypnea, accessory muscle use, pH, and $PaCO_2$) and if there is no improvement after initiation of therapy, patients should have their NIV settings adjusted or be intubated.

TABLE 60.3 Indications and Contraindications for Noninvasive Positive Pressure Ventilation and Invasive Mechanical Ventilation

	RESPIRATORY SUPPORT INDICATIONS	
	Bi-Level Noninvasive Ventilation	**Invasive Mechanical Ventilation**
Indications	• Respiratory acidosis ($PaCO_2$ ≥45 mm Hg and pH ≤7.35) • Severe dyspnea with signs of respiratory muscle fatigue and accessory muscle use • Persistent hypoxemia despite supplemental oxygen therapy	• Unable to tolerate NIV • NIV failure • Persistent diminished consciousness • Respiratory or cardiac arrest • Persistent inability to remove secretions • Hemodynamic instability without response to fluids and vasoactive medications • Life-threatening hypoxemia not corrected by less invasive interventions
Contraindications	• Active vomiting/high-risk aspiration • Respiratory arrest • Facial trauma • Depressed mental status not related to high $PaCO_2$	• Appropriate for NIV • Patient wishes (e.g., advanced directive, do not resuscitate or do not intubate order)

NIV, Noninvasive ventilation.

High-Flow Nasal Cannula

While high-flow nasal cannula (HFNC) oxygen therapy is primarily used in hypoxic respiratory failure,[41] it is increasingly being used in patients with COPD. Multiple small studies show an increase in oxygenation, reduction in hypercapnia, and comfort in stable patients with COPD.[42–44] While NIV remains the first-line therapy in hypercapnic respiratory failure in COPD, HFNC is a viable support modality for patients with mild to moderate respiratory acidosis who do not tolerate or need breaks from NIV[45–47] and do not require intubation and invasive ventilation. The same monitoring parameters as NIV apply to HFNC.

Invasive Ventilation

The decision to intubate a patient during a COPD exacerbation depends on the patient's condition (not laboratory values), failure of first-line therapy, and patient's wish. Indications for intubation and mechanical ventilation are outlined in Table 60.4. The mortality rate of patients with respiratory failure secondary to COPD exacerbation is high, but it is important to note that the mortality rate in COPD exacerbation patients is lower than in all comers with respiratory failure to the intensive care unit. Treatment recommendations should be based on the patient's values and disease burden. We advise against prognostication in the very early phase of the resuscitation. An immediate response to intubation and continued treatment is often not seen in the ED. Inaccurate prognostication may have downstream repercussions in the care of the patient later in the hospital admission or subsequent admissions.

The goals of mechanical ventilation are to decrease the patient distress and work of breathing, minimize dynamic hyperinflation and intrinsic PEEP, and to lessen hypercapnia and hypoxemia without exposing the patient to iatrogenic complications. No mode of

ventilation is superior to achieve these goals. Focus during the initial ventilation phase should be directed towards maintaining normoxia and preventing dynamic hyperinflation. Severe respiratory acidosis is common, and hypercapnia should be tolerated without adjusting the minute ventilation if the pH is greater than 7.2.

After the patient is initially intubated and while still sedated and paralyzed, an assist control mode of ventilation is required. We recommend volume assist control with an initial respiratory rate of 10 to 14 breaths/min, tidal volume of ≤8 mL/kg of predicted body weight, a square flow inspiratory waveform, inspiratory time of 0.8 to 1 seconds, PEEP of 5, and titration of inspired oxygen to a saturation of 88% to 92%. These patients commonly have long time constants and EFL and require a longer exhalation time to reach FRC. Dynamic hyperinflation risk is proportionally related to a high minute ventilation. Setting a respiratory rate of 10 to 14 breaths/min is the most effective way to decrease the minute ventilation and duty cycle time to prevent dynamic hyperinflation. Respiratory rates less than 10 breaths/min are not recommended. They allow for longer emptying, but may decrease the minute ventilation to an undesirable level causing a severe hypercapnic respiratory acidosis without a significant benefit in lowering end-expiratory lung volumes and pressures (Fig. 60.6).[16] Soon after

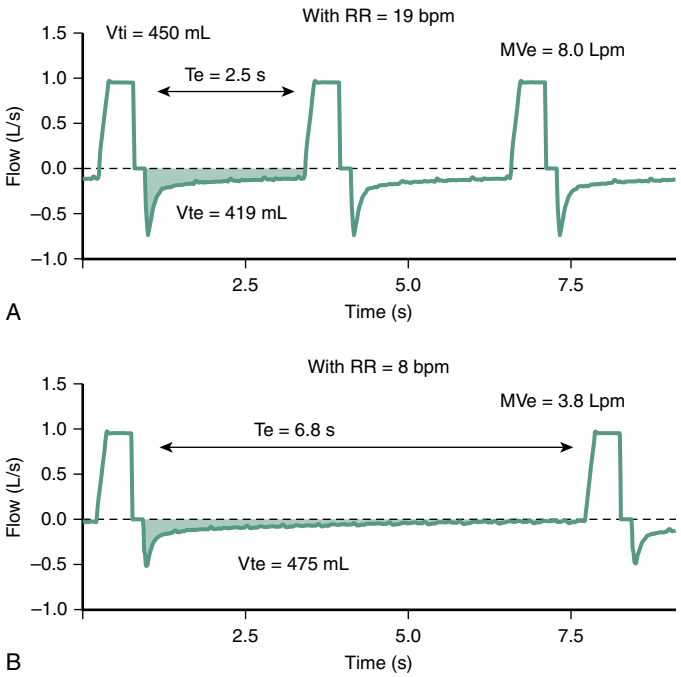

Fig. 60.6 Flow-time curves from a patient with chronic obstructive pulmonary disease with tidal expiratory flow limitation showing the result of prolonging expiration time. (A) Original ventilator settings in volume-controlled mode with a respiratory rate of 19 breaths/min, expiratory time *(Te)* of 2.5 seconds and the exhaled tidal volume *(Vte)* (area between the expiratory flow tracings and the x-axis) of 419 mL. This approach resulted in a total minute ventilation *(Mve)* of 8.0 liters per minute (Lpm) and the intrinsic positive end-expiratory pressure of 7.3 cm H_2O (not shown here). (B) The same patient with the respiratory rate reduced to 8 breaths/min while keeping the other parameters unchanged. This approach resulted in a Te of 6.8 seconds, more complete lung emptying (an end-expiratory flow virtually reached zero), and the intrinsic positive end-expiratory pressure decreased to less than 1 cm H_2O (not shown here). However, the additional Vte gained was less than 60 mL compared with the original settings, and the total MVe was decreased to 3.8 Lpm, which was clinically undesirable. (From Junhasavasdikul D, Telias I, Grieco DL, et al. Expiratory flow limitation during mechanical ventilation. *Chest*. 2018;154(4):948–962. https://doi.org/10.1016/j.chest.2018.01.046 https://doi.org/10.1016/j.chest.2018.01.046)

intubation, peak pressure, total PEEP, and plateau pressure should be measured. High peak pressures are expected because of high resistance in the airways. When there is an elevated peak pressure, greater than 40 to 45 cm H_2O, it is important to confirm that there are no quickly reversible causes of airway resistance such as a mucous plug, kinked or malpositioned endotracheal tube, or tension pneumothorax. Plateau pressures should also be measured at this time to evaluate pulmonary compliance, with a goal of less than 30 cm H_2O. High peak pressures and low plateau pressures reflect increased resistance with normal compliance of the respiratory system. In this scenario, peak pressures do not represent pressures at the alveoli. If the peak airway pressures are consistently above 40 to 45 cm H_2O without a reversible cause, and plateau pressures are low, we recommend adjusting the peak pressure alarm profile so the patient is not under-ventilated (if the peak pressure limit is reached, the flow will terminate resulting in a small tidal volume with a high dead space to alveolar ventilation ratio) and continue medical management while mechanically ventilated.

Dynamic hyperinflation occurs when the patient receives a breath before the respiratory system returns to FRC (i.e., completely exhales), which increases end-expiratory lung volumes and intrathoracic pressure. Signs of dynamic hyperinflation can be detected by evaluating the flow versus time waveform, the end-expiratory velocity, or measuring the total PEEP. The flow versus time waveform (Fig. 60.7) graphically displays inspiratory and expiratory flow throughout the respiratory cycle. If the expiratory flow limb does not reach zero prior to the next delivered breath, there will be dynamic hyperinflation because exhalation was not complete. Some ventilators display the end-expiratory velocity in liters/min, and a positive velocity at the end of the breath means they are exhaling at the time of the next breath.

Checking the total PEEP screens for dynamic hyperinflation and intrinsic or auto-PEEP (iPEEP). Total PEEP is measured after a 3 to 5-second end-expiratory hold on a passively breathing patient. The pressure reflects the externally applied (ventilator set) PEEP and the iPEEP (Fig. 60.8). For example, if the ventilator prescribed external PEEP is 5 cm H_2O and the total PEEP is 17 cm H_2O, the iPEEP or auto-PEEP is 12 cm H_2O. This increased pressure results from increased end-expiratory lung volumes and alveolar overdistension within the fixed thoracic space. Patients who are intubated during a COPD exacerbation without multiple pulmonary infiltrates should have a normal plateau pressure despite an increase in peak pressure. A high plateau pressure in the setting of an increase in iPEEP represents decreased compliance of an over distended lung. Increased expiratory lung volumes and iPEEP may cause hypotension from decreased preload. This

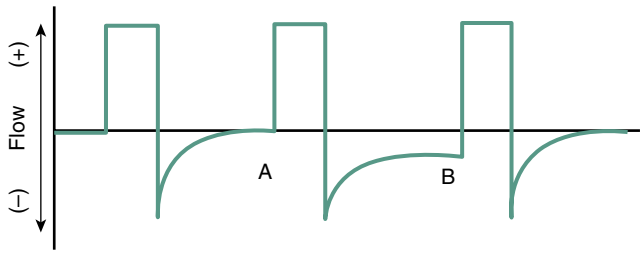

Fig. 60.7 **Flow Versus Time Ventilator Waveform.** Positive flow on the y-axis is the ventilator delivering a breath into the patient. Negative flow is the patient's passive exhalation. (A) depicts an expiratory flow limb returning to zero at the end of exhalation. The represents complete exhalation of the tidal volume and a return to the passive functional residual capacity. The curve and slope of the expiratory flow limb is determined by the passive recoil of the chest wall. (B) depicts an expiratory flow limb that does not return to zero prior to the next ventilator delivered breath. This represents the patient's continued and incomplete exhalation prior to the next delivered breath.

response is exaggerated in COPD because highly compliant lungs readily transmit the increased pulmonary pressures to the heart and great vessels. In the example above the total pressure in the chest transmitted to the great vessels is 17 cm H_2O (12.5 mm Hg).

Pressure assist control may also be used as an initial ventilator setting when a patient is sedated and paralyzed (also see Ventilatory Support, Chapter 2). We recommend starting with a pressure of 15 cm H_2O above PEEP and an inspiratory cycling time of 0.8 to 1 seconds. Inspiratory pressure and cycling time targets may be adjusted to deliver a tidal volume of approximately 8 mL/kg predicted body weight. Some patients may be more comfortable in a pressure-controlled mode because of an increased inspiratory flow, but there is no significant outcome difference among ventilation modes. When ventilating a patient in pressure assist control mode, it is essential to monitor tidal volumes to assure adequate ventilation because tidal volumes will vary depending on the resistance and compliance of the respiratory system.

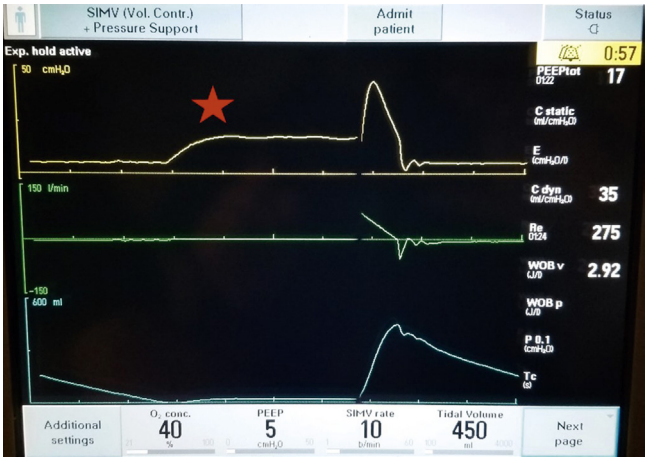

Fig. 60.8 Ventilator screen displaying an end expiratory hold with an elevated intrinsic positive end expiratory pressure (PEEP). The star marks an elevation in the pressure waveform with a corresponding total PEEP of 17 cm H_2O and set PEEP of 5 cm H_2O. The iPEEP in this case is 12 cm H_2O (total PEEP minus set PEEP). (Image courtesy of Dr. Skyler Lentz.)

Spontaneously breathing patients may be transitioned to pressure support ventilation. Many patients are comfortable in this mode of ventilation because they control inspiratory time and flow. We recommend an initial pressure support of 15 cm H_2O above PEEP titrated based on tidal volume and patient comfort. In any mode of ventilation, some patients may ineffectively trigger or cycle a mechanical breath causing ventilator dyssynchronies. If patients appear to be attempting to inhale or exhale in asynchrony with the ventilator, we recommend consulting an intensivist or pulmonologist. Ventilator troubleshooting steps are displayed in Table 60.4.

PEEP can be safely set to 5 cm H_2O for all patients with a COPD exacerbation. There is no significant benefit of decreasing the PEEP to 0 cm H_2O or increasing the PEEP in the early care of sedated and paralyzed patients. Further PEEP titration depends on individual patient's physiology. In most cases of patients with COPD who are intubated, EFL is present and PEEP may be increased to between 50% and 80% of the total PEEP. Increasing the PEEP does not decrease the expiratory flow because it is no longer determined by the absolute pressure

TABLE 60.4 Troubleshooting for Commonly Encountered Problems in Intubated Chronic Obstructive Pulmonary Disease Patients With Mechanical Ventilation

TROUBLESHOOTING VENTILATION DIFFICULTIES

Problem	Suggestion
Elevated end-tidal CO_2 or $PaCO_2$	Tolerate respiratory acidosis if the pH is >7.2 without adjusting the respiratory rate or tidal volume. Respiratory acidosis will improve with medical treatment and time while ventilated.
Elevated end-tidal CO_2 or $PaCO_2$ AND pH <7.2	1. If there is minimal iPEEP, increase the respiratory rate slowly and frequently check for iPEEP. 2. Should iPEEP develop, increase the tidal volume and keep the rate low. COPD does not require acute respiratory distress syndrome (ARDS) ventilation strategy. While the goal tidal volume is ≤8 mL/kg predicted body weight, if severe respiratory acidosis and obstructive shock from dynamic hyperinflation is a life threat start increasing the tidal volume.
High peak pressures	This is a reflection of increased airway resistance. Check a plateau pressure to evaluate compliance of the respiratory system. If the plateau pressure is low: 2. Evaluate for common causes of elevated peak pressures including kinked tubing, pneumothorax, mucous plugging, and mainstem intubation. 3. Continue bronchodilator therapy and tolerate high peak pressures. Increase peak pressure alarms to prevent hypoventilation.
High plateau pressures	If the patient does not have a reason to have a low compliance (e.g., multifocal pneumonia) this likely represents alveolar over distention from dynamic hyperinflation. Check a total PEEP and decrease the minute ventilation.
Elevated total PEEP or iPEEP	This represents dynamic hyperinflation. If hypotension is present remove the patient from the ventilator for approximately 10–15 s to allow adequate exhalation. Reduce the minute ventilation by decreasing the respiratory rate between 10 and 14 breaths/min.
Awakens from sedation or paralysis wears off	Clinical decision of transition to a pressure supported mode of breathing or increasing sedation. • If stable, patients will often tolerate pressure support ventilation with an initial setting of pressure support of 15 cm H_2O over a PEEP of 5 cm H_2O. The patient will determine their respiratory rate. Monitor for triggering or cycling dyssynchronies such as the patient trying to inhale or exhale and the ventilator not responding. • If a patient is unstable or has severe air trapping, increase sedation so the patient is synchronous with the ventilator. Reattempt sedation wean at a later time.

COPD, Chronic obstructive pulmonary disease; *iPEEP*, intrinsic positive end expiratory pressure.

gradient between the alveoli and ventilator and may improve expiratory flow by stenting open small collapsing airways. If any PEEP changes are made, it is important to follow the associated changes in peak pressure, total PEEP, and plateau pressure.

Disposition

Disposition decisions are based on a multitude of factors including severity of symptoms, presence of respiratory failure, response to treatment in the ED, presence of serious comorbidities, failure of outpatient treatment, and home resources/support. Patients who have significant symptom improvement in the ED with no signs of respiratory failure, no new oxygen needs, a normal laboratory evaluation, and no evidence of hemodynamic instability or cardiac ischemia, with adequate home support and a follow-up plan with a primary care or pulmonology provider are suitable for discharge home. We recommend education about inhaler or nebulizer use and close coordination with their primary care provider or pulmonologist. Patients with severe symptoms, including resting dyspnea, worsened hypoxia, tachypnea, drowsiness and confusion, or symptoms significantly worse than their baseline should be admitted to the hospital. If there are signs of respiratory failure and need for NIV, consultation with the intensive care unit is recommended (Box 60.3).

ED observation units (sometimes called short-stay units or clinical decision units) can provide short term care for COPD exacerbations in patients with non-severe symptoms who fail to improve significantly with initial treatment but are expected to improve within 48 hours. Observation units help decrease the number of patients requiring inpatient hospital admission.[48] Through protocolized care and the coordination of discharge services, observation unit stays can decrease the 30-day ED revisit rate without decreasing the number of patients discharged directly from the ED.[49] Patients with underlying severe disease, frequent recent hospitalizations, severe symptoms including new oxygen requirement, and abnormal chest x-ray findings suggestive of lobar pneumonia are unlikely to respond to treatment within a timeframe appropriate for an ED observation admission.[50]

BOX 60.3 General Guidelines for Admission of the Patient With Chronic Obstructive Pulmonary Disease

1. Significant worsening of symptoms from baseline
2. Inadequate response of symptoms to emergency department (ED) management
3. Significant comorbid conditions (e.g., pneumonia, heart failure)
4. Worsening hypoxia or hypercarbia (from baseline)
5. Inability to cope at home or insufficient home resources

Adapted from Vestbo J, Hurd SS, Agusti AG, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 187:351, 2013.

The references for this chapter can be found online at ExpertConsult.com.

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CHAPTER 60: QUESTIONS AND ANSWERS

1. A patient presents to the emergency department with 8 months of progressive dyspnea. There is no recent change in the patient's symptoms. On exam, there is a prolonged expiratory phase without wheezing, no rales, no pedal edema. The electrocardiogram is normal. The chest x-ray revealed hyperinflation with a flattened diaphragm. The diagnosis of chronic obstructive pulmonary disease (COPD):

a. Can be made clinically in this patient
b. Can be made radiographically with demonstration flattening of the diaphragms and hyperinflation on chest x-ray
c. Requires demonstration of spirometry-proven airflow limitation with the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) after bronchodilators less than or equal to 0.7
d. Requires genetic testing and historical features including increased cough, sputum production, noxious stimuli, and dyspnea

Answer: c. The diagnosis of COPD requires spirometry-proven airflow limitation defined as a ratio of FEV_1 divided by FVC after bronchodilators of less than 0.7. Patients who have normal spirometry with chronic symptoms and possible emphysema on CT scan are not considered to have COPD.

2. In a patient with a diagnosis of chronic obstructive pulmonary disease (COPD), increased dyspnea, sputum production, and sputum purulence worse than baseline day-to-day variations for the past three days requiring evaluation in the emergency department is defined as:

a. Chronic bronchitis
b. COPD exacerbation
c. Emphysema
d. Progression of underlying disease

Answer: b. COPD exacerbation can be defined as a worsening of symptoms from baseline day-to-day variations that requires treatment. The most common symptoms include increased dyspnea, cough, increased sputum production and increased sputum purulence.

3. A 64-year old male with a history of severe chronic obstructive pulmonary disease (COPD) with baseline 3 L/min oxygen requirement presents to the emergency department with complaint of dyspnea. On physical exam, he is taking rapid shallow breaths with a respiratory rate of 50, requiring 8 L/min by nasal cannula to maintain a SpO_2 of 88%, but is awake and following commands. A blood gas reveals a pH of 7.25 and a pCO_2 of 70 mm Hg. Chest x-ray reveals hyperinflated lungs without evidence of pneumothorax or infiltrate. Antibiotics, nebulized short-acting beta-agonists, and glucocorticoids are initiated. The next step in management is:

a. Continue medical management
b. Intubate the patient for anticipated clinical decline
c. Start noninvasive bi-level positive pressure ventilation
d. Trial high flow nasal cannula

Answer: c. This patient is presenting with respiratory failure without clear contraindications to noninvasive ventilation. The patient should be trialed on noninvasive ventilation and receive inhaled bronchodilators including albuterol and ipratropium, glucocorticoids, and antibiotics. Glucocorticoids have similar bioavailability and efficacy when given PO or IV, however in patients with respiratory distress we recommend avoiding oral medications.

CHAPTER 60: QUESTIONS AND ANSWERS—cont'd

4. The rapid, shallow breathing pattern that develops in a chronic obstructive pulmonary disease (COPD) exacerbation _____ exhalation time causing hyperinflation, and _____ the proportion of dead space ventilation causing hypercapnia and respiratory muscle fatigue.

a. Decreases, decreases
b. Decreases, increases
c. Increases, decreases
d. Increases, Increases

Answer: b. The rapid, shallow breathing pattern that develops in a COPD exacerbation decreases exhalation time causing hyperinflation and increases the proportion of dead space ventilation causing hypercapnia and respiratory muscle fatigue. If untreated, this will progress to respiratory failure.

5. When treating a patient with a chronic obstructive pulmonary disease (COPD) exacerbation who requires invasive mechanical ventilation, setting the initial tidal volume to 8 mL/kg predicted body weight and the respiratory rate to 10 to 14 breaths/min helps prevent the development of:

a. Acidosis
b. Dynamic hyperinflation
c. Hypercapnia
d. Expiratory flow limitation

Answer: b. Decreasing the respiratory rate in an intubated patient with COPD allows for complete emptying and return to FRC, decreasing the development of dynamic hyperinflation and auto-positive end expiratory pressure (PEEP).