Acute exacerbation of chronic obstructive pulmonary disease
**Summary**

An acute exacerbation of chronic obstructive pulmonary disease (COPD) typically presents with an increased level of dyspnea, worsening of chronic cough, and/or an increase in the volume and/or purulence of the sputum produced.

An exacerbation may represent the first presentation of COPD, and COPD is usually associated with a history of tobacco exposure.

Treatment includes bronchodilators, systemic corticosteroids, oxygen, and antibiotics. Some patients with more severe exacerbations may require ventilatory support.

Antibiotics are reserved for exacerbations thought to be due to bacteria. An increase in sputum purulence, plus an increase in sputum volume, and/or increased dyspnea, indicates a need for antibiotics.

Treatment may be complicated by the development of hyperglycemia (associated with the use of corticosteroids) and/or diarrhea, including *Clostridium difficile*-associated diarrhea (associated with the use of antibiotics).

**Definition**

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 and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases, and influenced by host factors, including abnormal lung development."[1]

An exacerbation of COPD may be defined as "an acute worsening of respiratory symptoms that results in additional therapy."[1]
Epidemiology

COPD is the fourth leading cause of death worldwide, and the third leading cause of death in the United States.[1] [3] The death rate due to COPD increased over 100% between 1970 and 2002.[4] No other major cause of death in the US has increased at this rate. Globally, COPD has been shown to be responsible for 3.8% of deaths in high-income countries and 4.9% of deaths in low-income countries.[5] There is significant variability in the prevalence of COPD between countries.[6] [7] [8] This may be due to differing rates of exposure to tobacco smoke and indoor and occupational pollutants.[5] In the past, men have experienced higher rates of disease due to COPD. This difference has been thought to be due primarily to greater exposure to tobacco smoke and occupational pollutants. Surveys have shown that the prevalence of COPD appears to be becoming more equally distributed between men and women.[7] [9] COPD contributes a significant burden of healthcare costs.[6] Exacerbations are responsible for much of the morbidity and mortality experienced by people with COPD, and the median number per year ranges between 1 and 3.[10] [11] It has been clearly shown that patients with more severe manifestations of COPD have greater rates of mortality over time.[6] However, estimates of mortality may be underestimated, as deaths in this population are often attributed to other etiologies such as other respiratory disorders, lung cancer, and cardiovascular disease.[6]

Acute exacerbations of COPD are commonly triggered by viral or bacterial pathogens, pollutants, GERD, or changes in temperature and humidity, and present with an acute-onset, sustained worsening of the patient's respiratory symptoms, lung function, functional status, and quality of life.[10] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] Exacerbation rates and all-cause mortality tend to be higher during winter months.[23] Acute exacerbations of COPD, particularly those that are moderate to severe, have significant public health impact, with increased healthcare utilization and healthcare costs and increased mortality.[24] [25] [26] [27] [28] Early deaths among patients hospitalized with severe COPD exacerbation are often caused by concurrent problems such as pulmonary embolus, pneumonia, or congestive heart failure.[29] Patients may also be at risk of myocardial infarction and stroke in the post-exacerbation period.[30]

Etiology

The most common cause of COPD in the developed world is exposure to tobacco smoke. Data have shown that, over time, 50% of chronic smokers develop COPD.[6] [31] The development of COPD is a complex process that is not completely understood. Inflammation, oxidant-antioxidant imbalance, protease-antiprotease imbalance, and several additional processes including recurrent infection, immunosenescence, autoimmunity, altered tissue healing, and other mechanisms are all implicated in the pathogenesis of COPD. While tobacco smoking is a well-recognized cause of COPD, the risk for developing COPD may also depend on sex, genetic and socioeconomic factors, as well as exposures to dusts, chemicals, and pollutants, early childhood severe respiratory infection, and failure to reach optimal lung growth by early adulthood.

Acute exacerbations of COPD occur intermittently throughout the course of the disease over the patient’s lifetime. Exacerbations vary in severity and are thought to be triggered primarily by infections (both viral and bacterial) and airborne pollutants.[32] In approximately one third of COPD exacerbations, no clear cause can be identified. A careful search for other causes of respiratory decompensation (e.g., congestive heart failure or pulmonary embolus) should be considered in such patients.[5] [6]

During an episode, decreases in the FEV1, forced vital capacity (FVC), and peak expiratory flow (PEF) may be identified and are due at least in part to airway inflammation.[10] [32] [33] However, exacerbations are diagnosed primarily by the identification of typical signs and symptoms rather than by spirometry.[34]
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Theory

Whereas previously, bacterial infections were thought to be the predominant cause of COPD exacerbations, use of newer molecular techniques has demonstrated the importance of viral infections as triggers.[35] It has been estimated that respiratory viruses are responsible for 22% to 64% of acute exacerbations.[36] [35] The most common bacterial pathogens include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. [32] [37] Atypical bacterial pathogens, such as *Mycoplasma* and *Chlamydia pneumoniae*, are also thought to trigger exacerbations, as are respiratory viruses such as rhinovirus, influenza, respiratory syncytial virus, parainfluenza virus, and human metapneumovirus.[38] [36] [39] [40] [41] [35] The severity of baseline lung function impairment influences the profile of pathogens most likely to be present.[37]

Exacerbations may also be due to environmental pollutants such as smoke particulate matter, sulfur dioxide, nitrogen dioxide, and ozone, as well as exposure to other irritants, such as cleaning products, hair salon products, and other chemicals.[42] [43] [44] [45]

GERD contributes to COPD exacerbations for some people.[18] [19] [20] [21] [22]

Pathophysiology

Smoking, or other significant exposure to smoke, is noted in most people with COPD. Components of smoke lead to impaired integrity of the tight junctions between lung epithelial cells, stimulate inflammation, and have been shown to decrease respiratory tract mucociliary clearance, increasing the likelihood of microbial pathogens penetrating the normally sterile lower respiratory tract.[46] [47] [48] [49] The presence of microbial flora leads to antigen presentation and stimulation of the innate and then the adaptive immune response.[50] Over time, chronic irritation by smoke and the inflammatory response leads to emphysema, hypertrophy of airway mucus glands, small airway fibrosis, and a decrease in the elastic recoil of the lung.[51] The decrease in elastic recoil (due to emphysema) and/or obstruction of the small airways due to inflammation, edema, and hypersecretion of mucus leads to decreased FEV1 and FEV1/FVC.[52] Hyperinflation that results from airflow limitation is a main cause of dyspnea.[53] Unlike asthma, airflow limitation in COPD is not fully reversible with medical therapy.[54] Furthermore, while the pathogenesis of both asthma and COPD is rooted in inflammation, the specific inflammatory process differs between these disorders.[11] However, a substantial number of patients with COPD do have a component of airflow obstruction that is reversible with bronchodilator therapy.[55] Indeed, inhaled bronchodilators (beta-2-agonists and anticholinergics) are one of the primary forms of therapy for all patients with COPD, because, in addition to bronchodilation, they have also been shown to decrease dynamic hyperinflation.[56] [57]

Acute exacerbations of COPD may be defined as an acute worsening of respiratory symptoms (e.g., dyspnea, cough, sputum production) that results in the need for additional therapy.[1] This worsening appears to result from increases in airway inflammatory cells and proteins that are triggered by an infection, airborne pollutants, and/or other factors.[33] [58] [59] [60] [18] [19] [20] [21] [22] The acute on chronic inflammatory response and/or concurrent bronchoconstriction leads to worsening in expiratory airflow limitation.[13] Worsening of expiratory airflow limitation leads to increased resistive work of breathing, increased ventilation/perfusion mismatch, and gas exchange disturbances. It also results in increased hyperinflation, which then further worsens lung mechanics and can lead to impaired function and fatigue of the respiratory muscles.[13] Due to the difficulty in obtaining specimens from people with exacerbations of COPD, further complicated by heterogeneous triggers, knowledge of the inflammatory response during an episode is incomplete.
Acute exacerbations have significant impact on activity level, functional status, and quality of life experienced by people with COPD. Moreover, recovery from exacerbations may be prolonged, and some patients never regain their prior level of lung function and/or functional status. There is evidence to suggest that exacerbations not only tend to be more frequent and more severe as COPD progresses, but may themselves accelerate the decline in lung function in COPD. Indeed, some patients may also be at increased risk for COPD exacerbations (i.e., have a phenotype of increased susceptibility) independent of disease severity. Currently recommended assessment of COPD patients includes confirmation of the diagnosis, determination of the severity of the airflow obstruction, assessment of symptoms, as well as assessment of the risk of exacerbations. People with severe or very severe airflow obstruction, those with a history of two or more exacerbations in the preceding year, or those with history of hospitalization due to exacerbation in the previous year are considered at high risk of subsequent exacerbations. Several additional factors are also associated with exacerbations and/or hospitalizations for COPD. COPD exacerbations, particularly those requiring hospitalization, are associated with increased mortality, as well as significant healthcare costs.

Classification

Global Initiative for Chronic Obstructive Lung Disease criteria

In pulmonary function testing, a postbronchodilator FEV1/FVC ratio of <0.70 is commonly considered diagnostic for COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) system categorizes airflow limitation into stages. In patients with FEV1/FVC <0.70:

- GOLD 1 - mild: FEV1 ≥80% predicted
- GOLD 2 - moderate: 50% ≤ FEV1 <80% predicted
- GOLD 3 - severe: 30% ≤ FEV1 <50% predicted
- GOLD 4 - very severe: FEV1 <30% predicted.

The GOLD guideline uses a combined COPD assessment approach to group patients according to symptoms and previous history of exacerbations. Symptoms are assessed using the Modified British Medical Research Council (mMRC) or COPD assessment test (CAT) scale.

- Group A: low risk (0-1 exacerbation per year, not requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT <10)
- Group B: low risk (0-1 exacerbation per year, not requiring hospitalization) and more symptoms (mMRC≥ 2 or CAT≥ 10)
- Group C: high risk (≥2 exacerbations per year, or one or more requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT <10)
- Group D: high risk (≥2 exacerbations per year, or one or more requiring hospitalization) and more symptoms (mMRC≥ 2 or CAT≥ 10).

Case history

Case history #1

A 67-year-old woman with a history of COPD presents with 3 days of worsening dyspnea and increased frequency of coughing. Her cough is now productive of green, purulent sputum. The patient has a 100-
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She has had a pack-year history of smoking. She has had intermittent, low-grade fever of 100°F (37.7°C) for the past 3 days and her appetite is poor. She has required increased use of rescue bronchodilator therapy in addition to her maintenance medications to control symptoms.

Other presentations

COPD often goes unrecognized. By the time that COPD is diagnosed, patients typically experience dyspnea with only mild to moderate exertion and may have a chronic productive cough, and FEV1 is often already <50% of predicted level. Many patients are diagnosed with COPD for the first time when they require hospitalization for an acute exacerbation of disease.[2] Exacerbations may be triggered by an infection or exposure to an airborne pollutant or other change in environmental conditions. Patients commonly present with a complaint of increased dyspnea, a change in the intensity and frequency of chronic cough and/or wheezing, and a change in the color and/or volume of sputum produced. Patients experiencing an exacerbation may have a low-grade fever, but the presence of a fever, especially >101.3°F (>38.5°C) should increase suspicion for an alternate diagnosis such as pneumonia.
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**Diagnosis**

**Approach**

Many definitions for acute exacerbations of COPD have been proposed and include many of the same components. Episodes may be diagnosed in people with a history of COPD who experience any of the following: worsening respiratory symptoms and physiologic status; or worsening of degree of cough, level of dyspnea, and/or the volume and character of sputum, particularly if these changes are acute in onset, sustained over time, beyond the normal day-to-day variation, or lead to a change in the patient’s baseline medication regimens.[10] [76] [1] [107] [108] [109]

Exacerbations are defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as mild, moderate, or severe.[1] Severe exacerbations may have associated acute respiratory failure and should be dealt with in hospital. Mild and moderate exacerbations may be dealt with in primary care or as an outpatient.

**Clinical evaluation**

Most patients presenting with a potential acute exacerbation are stable enough that they may be evaluated and managed in the outpatient setting. Clinical evaluation should include determination of the following:

- vital signs (including oxygen saturation via pulse oximetry or ABG)
- mental status
- severity of the level of dyspnea and airflow obstruction
- history of symptoms associated with the patient’s chief complaints
- the ability to continue to provide self-care at home.

The patient’s medical record should be reviewed to check for recent spirometry results confirming a diagnosis of COPD. If there is no recorded spirometry result, and the patient is admitted to hospital for an exacerbation, spirometry should subsequently be arranged to confirm the diagnosis of COPD. Consideration should also be given as to whether there are other findings (e.g., history of chronic bronchitis symptoms, and/or emphysema or chronic inflammatory airways disease evident on CT imaging) to suggest a diagnosis of COPD.

The risk of exacerbations should also be assessed: people with severe or very severe airflow obstruction, those with a history of two or more exacerbations in the preceding year, or those with history of hospitalization due to exacerbation in the previous year are considered at high risk of subsequent exacerbations.[1]

Patients should be questioned regarding:

- changes in their baseline level of dyspnea, cough, wheeze, and sputum production
- character of the sputum
- presence of fever
- any other focal complaints (e.g., chest pain, signs/symptoms of an upper respiratory tract infection, palpitations, lightheadedness, or leg swelling)
- their understanding and adherence with their current medical regimen for COPD, including the use of supplemental oxygen and any change in their requirement for rescue inhaler use.

On examination, auscultation may reveal wheeze, and it is important to observe patients for signs of respiratory failure (e.g., tachypnea, accessory muscle use, chest retractions, paradoxical movements of the abdomen, silent chest, confusion, drowsiness, and/or cyanosis), and/or signs of cor pulmonale, hemodynamic instability, or worsened mental status.
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Prognostic scores, such as the DECAF score (Dyspnea, Eosinopenia, Consolidation, Acidemia, and atrial Fibrillation), can be used to assess the severity of the exacerbation. The DECAF score is a predictor of inpatient mortality among hospitalized patients with COPD, and potentially a means of determining which patients may be safely treated for their acute exacerbations in the home setting.[110][111]

**Laboratory evaluation and imaging**

Diagnostic tests are typically reserved for those with moderate to severe exacerbations. Features of a more severe exacerbation include, but are not limited to, unstable vital signs, severe symptoms, low oxygen saturation on pulse oximetry, evidence of ventilatory failure, or mental status change (e.g., confusion, lethargy, coma). Diagnostic testing should also be considered if the diagnosis of an episode is uncertain.

Diagnostic tests for people with moderate to severe exacerbations may include:

- Pulse oximetry: at rest, with exertion, and/or during sleep
- Chest x-ray: may show hyperinflation, flattened diaphragms, increased retrosternal airspace, bullae, and a small, vertical heart; CT scan may be considered to characterize the features of COPD and to exclude other conditions, such as pulmonary embolism or tracheobronchomalacia
- ECG
- ABG
- CBC with platelets
- Electrolytes
- Creatinine
- BUN levels
- Sputum analysis.

Sputum cultures or endotracheal aspirates (in patients who are intubated) are recommended for the assessment of bacterial infection in patients with severe lung function impairment, those with a history of frequent exacerbations, and/or in patients hospitalized with COPD exacerbations or who require mechanical ventilation, as gram-negative bacteria (such as *Pseudomonas* species) or resistant pathogens may be present.[1][37] Consideration may also be given to obtaining a sputum culture in patients who have bronchiectasis and suspected infectious exacerbations as a feature of their COPD.

Where feasible, tests for respiratory viruses should be conducted in hospitalized patients, to prevent healthcare-associated transmission of the pathogen (e.g., influenza, respiratory syncytial virus, and parainfluenza virus). While it is unclear whether SARS-CoV-2 (the virus that causes COVID-19) can precipitate exacerbations of COPD, it is presumed that this will be found to be the case, similar to other respiratory viruses. When SARS-CoV-2 is known to be circulating in the community, patients presenting with an exacerbation of COPD should be isolated due to the great overlap in symptoms between COVID-19 and other acute respiratory tract infections and exacerbations. In the hospital setting, patients with an exacerbation of COPD should be pre-emptively isolated and tested for SARS-CoV-2.[1]

**Emerging investigations**

Procalcitonin is emerging as a promising biomarker for the diagnosis of bacterial infections as it tends to be higher in severe bacterial infections and low in viral infections. The Food and Drug Administration has approved procalcitonin as a test for guiding antibiotic therapy in patients with acute respiratory tract infections. A Cochrane review of the use of procalcitonin to guide initiation and duration of antibiotic treatment in people with acute respiratory tract infections found it lowered the risk of mortality, and lead...
to lower antibiotic consumption, and lower risk for antibiotic-related side effects in all patients including those with acute exacerbation of COPD.[112] Further research is required to establish its use in clinical practice.[1] Importantly, procalcitonin-guided antibiotic use is not recommended for COPD exacerbations in the intensive care unit setting, as this has been associated with increased mortality.[113]

C-reactive protein (CRP) is also being investigated as a potential biomarker to guide the use of antibiotics during exacerbations of COPD. A decision to withhold antibiotics, based on low CRP levels at the point of care, has been associated with reduced antibiotic prescriptions without worse clinical outcomes.[114] [115] [116]

### History and exam

#### Key diagnostic factors

**dyspnea (common)**
- A sustained increase from the baseline level of dyspnea beyond day-to-day variation is usually observed in patients with an acute exacerbation.[10]

**cough (common)**
- A change in the character and frequency of cough is often identified.[10] This change should be beyond day-to-day variations of the patient’s typical cough.[1]

**wheeze (common)**
- All patients with COPD have expiratory flow limitation, and this may lead to wheezing. Patients experiencing an acute exacerbation may be found to have greater severity of wheezing and prolongation of the expiratory phase of breathing on examination. However, wheezing is not identified in many patients.

**changes in sputum volume/color/thickness (common)**
- Changes in either volume or character (thickness, color) or both are frequently observed. The presence of purulent sputum appears to be sensitive and specific for high bacterial loads and may help identify subsets of patients who may most benefit from therapy with antibiotics.[118] [119]

**tachypnea (common)**
- Tachypnea is frequently seen and may be severe. It is important to observe the patient for signs of respiratory failure.

**cyanosis (uncommon)**
- Possible sign of impending respiratory failure.

#### Other diagnostic factors

**past medical history of COPD (common)**
- A past medical history of COPD should be sought, as well as of other conditions that may impact the likelihood of another acute problem considered in the differential diagnosis. People with a history
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of two or more exacerbations in the preceding year or those with history of hospitalization due to exacerbation in the previous year are considered at high risk of subsequent exacerbations.[1]

tobacco use (common)

• It is important to determine if patients have a history of significant exposure to tobacco or other smoke, and whether they are currently smoking, using e-cigarette/vaping products, or other inhaled substances (e.g., marijuana, cocaine, hookah/shisha).

past medical history of gastroesophageal reflux/swallowing dysfunction (common)

• It is important to determine if patients have a history of heartburn, bitter/sour taste in the mouth, coughing or choking after eating, hiatal hernia, and/or gastroesophageal reflux or difficulty swallowing.[18] [19] [20] [21] [22] However, GERD should be considered as a potential cause of recurrent exacerbations even if the patient lacks the above-noted typical symptoms and signs of gastroesophageal reflux. Nighttime episodes of coughing may also signal the presence of GERD.

• No available studies guide whether the treatment of reflux improves exacerbations of COPD.

malaise and fatigue (common)

• These symptoms and other nonspecific symptoms such as insomnia, decreased activity level and loss of appetite are commonly identified in people with an acute exacerbation of COPD.[108] [117]

• While these symptoms have great impact on the quality of life of the patient, they are generally not used to determine whether an exacerbation is present.

chest tightness (common)

• This may result from worsened airflow limitation and chest hyperinflation.[13] However, the possibility of a myocardial infarction or pneumothorax should be considered if marked chest tightness or other chest discomfort is present.

features of cor pulmonale (common)

• This may develop as a result of increased hypoxic vasoconstriction due to exacerbation-induced hypoxemia. The resulting increase in pulmonary vascular resistance and/or pulmonary artery pressure can lead to acute right heart failure. Elevated jugular venous pressure, hepatojugular reflux, peripheral edema, and relative hypotension may be present.

environmental/occupational exposure to pollutants or dust (uncommon)

• It should be determined whether the patient has a history of significant exposure to black smoke, such as wood smoke, dust, and/or other pollutants, such as chemicals or small particulate matter.

change in mental status (uncommon)

• Including drowsiness, confusion, and/or personality change.

fever (uncommon)

• In general, <50% of people with acute exacerbations of COPD experience fever.[28] [37] [40]

• The presence of a high and/or persistent fever should lead to consideration of the presence of bacterial pneumonia, influenza virus, or other infection.

accessory muscle use (uncommon)

• Sign of impending respiratory failure.
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paradoxical movements of abdomen (uncommon)

• Sign of impending respiratory failure.

Risk factors

Strong viral infection

• It has been estimated that respiratory viruses are responsible for 22% to 64% of acute exacerbations.[36] [35] Whereas previously, bacterial infections were thought to be the predominant cause of COPD exacerbations, the use of newer molecular techniques has demonstrated the importance of viral infection as triggers.[35]

• The rhinovirus has been isolated from patients with acute exacerbations of COPD more often than other viruses.[66]

• Influenza, respiratory syncytial virus, parainfluenza, coronavirus, adenovirus, and human metapneumovirus have also been associated with episodes.[37] [39] [40] [67] [41]

• Exacerbations associated with respiratory viruses have been shown to be more severe, and take longer to resolve, compared with those attributed to other triggers.[66] [68] Co-infection with viruses and bacterial pathogens is not uncommon. Coronaviruses are known triggers of COPD exacerbations.[69] [35] While it is unclear whether SARS-CoV-2 (the virus that causes COVID-19) can precipitate exacerbations of COPD, it is presumed that this will be found to be the case, similar to other respiratory viruses.[1]

• It has been hypothesized that the chronic presence of respiratory viruses in the lower respiratory tract may play a role in the pathogenesis of COPD.[70]

bacterial infection

• Bacterial infections are thought to be a common trigger of exacerbations, although interactions between host factors, bacteria, viruses, and changes in air quality are also thought to cause, or contribute, toward exacerbations.[1] [71] Evidence suggests that the presence of purulent sputum is frequently associated with a bacterial lower respiratory tract infection.[28] Because the lower respiratory tract in people with COPD may not be sterile, the interpretation of culture results of both upper and lower respiratory tract specimens must be made with caution. There is mixed evidence as to whether greater bacterial colony counts over baseline levels are present in patients with an acute exacerbation of COPD.[72] [73]

• The most frequently identified bacterial pathogens include Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis.[37] [59] The role of other gram-positive pathogens such as Staphylococcus aureus and gram-negative pathogens such as Pseudomonas aeruginosa in the pathogenesis of acute exacerbations of COPD is less certain, but patients with more severe COPD and greater frequency and/or severity of exacerbations, or those who have been hospitalized recently or had recent (within 2 weeks) daily use of systemic corticosteroids (i.e., >10 mg/day of prednisone) are more likely colonized with these pathogens.[37] [74]

• It has been shown that acquisition of a new strain of bacteria by people with COPD is a risk for an acute exacerbation.[75] Alterations in the innate and/or adaptive immune response may result in cyclical perpetuation of inflammation and infection.[50]

• Concurrent infection with both bacterial and viral respiratory tract pathogens has been associated with more severe episodes.[58] Treatment of moderate to severe exacerbations with antibiotics has been
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Influenza vaccination may have a protective effect in reducing risk of *Pseudomonas aeruginosa* infection.[37]

**gastroesophageal reflux/swallowing dysfunction**

- Gastroesophageal reflux and swallowing dysfunction with associated aspiration are common triggers for exacerbations of COPD.[18] [19] [20] [21] [22] No available studies guide whether the treatment of reflux improves exacerbations of COPD.

**smoking**

- Avoiding smoke and smoking cessation are the best measures not only to prevent the onset of COPD, but also to prevent progression of the severity of COPD.[78] [79] Smoking cessation can also reduce the risk of exacerbations. Smoking cessation, counseling, and treatment are all recommended for people with COPD.[80] [81] Avoidance of all forms of inhaled irritants (including e-cigarettes/vaping, inhaled marijuana, cocaine, hookah/shisha, and other environmental irritants) is also recommended.[1]

**air pollutants**

- Increasing levels of air pollutants, specifically nitrogen dioxide (NO2), sulfur dioxide (SO2), ozone (O3), and black smoke particulates including wood smoke, have been associated with a greater rate of acute exacerbations and hospital admissions for people with COPD.[85] [86] [87] Peaks of air pollution can also increase hospitalizations and mortality.[88]

- Exposure to many of these pollutants has been found to induce an inflammatory response in the respiratory tract.[32] Exposure to other irritants, such as cleaning products, hair salon products, and other chemicals, also pose a risk for COPD exacerbation.[45]

**Weak**

**atypical bacterial infection**

- Atypical organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species) have been associated with acute exacerbations though with conflicting results.[82] [83] [84] There is insufficient evidence to suggest that antimicrobial coverage of atypical bacterial pathogens improves outcomes.

**change in weather**

- Changes in temperature and humidity are associated with increased risk for acute exacerbations of COPD.[32] [89] However, it remains unclear whether changes in ambient temperature and/or humidity or changes in risk for infection due to respiratory viruses and/or other pathogens account for this association.

- Exacerbation rates and all-cause mortality tend to be higher during winter months.[23]
# Investigations

## 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>oxygen saturation on pulse oximetry</strong></td>
<td>• Recommended to be performed for all patients with a possible acute exacerbation of COPD, when available. It should be performed when vital signs are obtained. During an episode, oxygen saturation is frequently depressed below the patient's baseline level, and supplemental oxygen and arterial blood gas testing should be considered if the level is &lt;90%.</td>
</tr>
<tr>
<td></td>
<td>depressed below the patient's baseline level</td>
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<tr>
<td><strong>chest x-ray</strong></td>
<td>• Rarely diagnostic; principal purpose is to exclude alternate diagnoses. A chest x-ray should be performed in people with moderate to severe disease and where pneumonia or other potential diagnoses (e.g., pneumothorax, congestive heart failure, pleural effusion) are being considered.</td>
</tr>
<tr>
<td></td>
<td>hyperinflation, flattened diaphragms, increased retrosternal airspace, bullae, and a small, vertical heart</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>• Cardiovascular disease is common in people with COPD.[120] Additionally, the possibility of a myocardial infarction, pneumothorax, or pulmonary embolus should be considered if chest tightness or other chest discomfort is present. Patients with COPD are at higher risk to develop cardiac ischemia and/or arrhythmias that can also lead to dyspnea.</td>
</tr>
<tr>
<td></td>
<td>may be right heart enlargement or right ventricular strain, arrhythmia, ischemia</td>
</tr>
<tr>
<td><strong>ABG</strong></td>
<td>• ABG testing should be performed for people with a moderate to severe acute exacerbation of COPD, to detect chronic hypercarbia and assess for acute respiratory acidosis. Comparison of results to prior baseline ABG is crucial (when available). Acute respiratory acidosis may be a sign of impending respiratory failure. Venous blood gas sampling is not considered a reliable alternative measure.[121] [ PaO2 &lt;60 \text{ mmHg} ] indicates potential respiratory failure. [ PaO2 &lt;50 \text{ mmHg}, PaCO2 \geq 45 \text{ mmHg}, \text{ or pH} &lt;7.35 ] indicate a potentially life-threatening illness that requires consideration for intensive care and initiation of assisted ventilation.[122]</td>
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<tr>
<td></td>
<td>respiratory acidosis and compensatory metabolic alkalosis</td>
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<td><strong>CBC with platelets</strong></td>
<td>• Should be considered for patients with moderate to severe exacerbations to screen for abnormalities that may suggest additional medical disorders such as infection or anemia.</td>
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<tr>
<td></td>
<td>may show elevated hematocrit, elevated WBC count or anemia</td>
</tr>
<tr>
<td><strong>electrolytes, BUN, + creatinine</strong></td>
<td>• Should be considered for patients with moderate to severe exacerbations. An abnormal result may suggest additional medical disorders. Patients with COPD exacerbations may have decreased oral intake and may become volume depleted. Patients with renal insufficiency may have metabolic acidosis that can increase ventilatory demand.</td>
</tr>
<tr>
<td></td>
<td>usually normal</td>
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</tbody>
</table>
# Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sputum culture + Gram stain</strong></td>
<td>may suggest bacterial infection</td>
</tr>
<tr>
<td>• In severe disease, and if the patient's sputum is purulent and hospitalization is being considered, a sputum Gram stain and culture should be obtained to assess for potential bacterial pathogens that may have triggered the episode.</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory virus diagnostics</strong></td>
<td>may confirm viral infection</td>
</tr>
<tr>
<td>• In severe disease and, if hospitalization is being considered, testing for respiratory virus pathogens (where feasible) should be considered both to identify any treatable agent (e.g., influenza), and to identify the need for use of expanded infection control precautions.</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac troponin</strong></td>
<td>normal if no myocardial injury</td>
</tr>
<tr>
<td>• Elevations in cardiac troponin can occur due to unrecognized myocardial injury resulting from COPD exacerbation. Elevations in troponin may be associated with increased mortality.</td>
<td>normal if no myocardial injury</td>
</tr>
<tr>
<td><strong>CT scan of chest</strong></td>
<td>normal if no pneumonia, pleural effusion, malignancy, pulmonary embolus, or tracheobronchomalacia present</td>
</tr>
<tr>
<td>• May be useful to exclude alternate diagnoses, including tracheobronchomalacia and especially pulmonary embolus, if the diagnosis and basis of respiratory decompensation remains uncertain after routine chest x-ray.</td>
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</table>

## Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td><strong>Procalcitonin</strong></td>
<td>may be elevated in severe bacterial infections and low in viral infections</td>
</tr>
<tr>
<td>• Emerging as a promising biomarker for the diagnosis of bacterial infections as it tends to be higher in severe bacterial infections and low in viral infections. The Food and Drug Administration has approved procalcitonin as a test for guiding antibiotic therapy in patients with acute respiratory tract infections. A Cochrane review of the use of procalcitonin to guide initiation and duration of antibiotic treatment in people with acute respiratory tract infections found it lowered the risk of mortality, and lead to lower antibiotic consumption, and lower risk for antibiotic-related side effects in all patients including those with acute exacerbation of COPD.[112] Further research is required to establish its use in clinical practice. It should not be used to guide antibiotic use in patients with severe COPD exacerbations requiring intensive care.[113]</td>
<td></td>
</tr>
<tr>
<td><strong>C-reactive protein</strong></td>
<td>may be elevated in bacterial infections</td>
</tr>
<tr>
<td>• C-reactive protein (CRP) is also being investigated as a potential biomarker to guide the use of antibiotics during exacerbations of COPD. A decision to withhold antibiotics, based on low CRP levels at the point of care, has been associated with reduced antibiotic prescriptions without worse clinical outcomes.[114] [115] [116]</td>
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# Acute exacerbation of chronic obstructive pulmonary disease

## Diagnosis

### Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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</thead>
</table>
| Congestive heart failure | • Patients with systolic left-sided or biventricular congestive heart failure will often have a history consistent with heart failure. Underlying diastolic heart failure is often under-recognized.  
• Physical examination may note signs consistent with heart failure, such as an elevated jugular venous pressure, extra heart sounds, coarse breath sounds with crackles above the lung bases, wheezing, and dependent pitting edema. [124] It may be difficult to distinguish systolic or diastolic heart failure from an acute exacerbation of COPD. Notably, heart failure can lead to increased work of breathing, and result in acute respiratory failure that may or may not be superimposed on chronic respiratory failure. | • Chest imaging may show an enlarged heart, pulmonary vascular congestion, and/or pleural effusions. An elevated B-type natriuretic peptide is often present. [125] [126] An echocardiogram may be used to determine cardiac function. |
| Pneumonia            | • Many aspects of acute exacerbations of COPD, including dyspnea, cough, and sputum production may be found in patients with pneumonia and it is often not possible to differentiate without chest imaging.  
• About 10% to 15% of patients presenting with an apparent acute exacerbation are found to have pneumonia, or other abnormalities, defined by chest imaging. [127] [128] [129] Patients with pneumonia have in general been found to experience higher fevers, more acute onset of illness, and somewhat greater severity of acute illness when compared with COPD patients without | • Chest imaging in patients with pneumonia should identify changes consistent with an infiltrative process in the lung parenchyma. |
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>The presence of pneumonia as a cause of respiratory decompensation in a patient with COPD does not necessarily imply the presence of a COPD exacerbation per se (i.e., the presence of worsened airflow limitation related to airways inflammation and/or bronchoconstriction), and as such careful consideration should be given as to whether systemic corticosteroids are warranted in such patients.</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>• Pleural effusions may exacerbate dyspnea in patients with COPD. Physical examination may demonstrate decreased or absent breath sounds with dullness to percussion related to a pleural effusion.</td>
<td>• Chest imaging is recommended.</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>• Patients with COPD found to have pneumothoraces may or may not have additional signs or symptoms suggestive of a respiratory tract infection, but their presentation may closely mirror that of an acute exacerbation. Decreased breath sounds may be identified on the affected side and tracheal deviation away from the affected side and/or hypotension may be present in patients with a tension pneumothorax.</td>
<td>• Chest imaging is recommended to exclude a possible pneumothorax in patients with more than mild episodes.</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>• Clinically, pulmonary embolism may present with signs and symptoms similar to an acute exacerbation of COPD, and the two are difficult to distinguish. Pulmonary embolism should be considered as a cause of the acute symptoms if no other identifiable trigger for the exacerbation is evident. People with prior pulmonary embolus may be diagnosed using D-dimer assay, spiral computed tomography angiogram, or pulmonary angiography in patients with COPD. Test selection should be based on local expertise. Dopplers of the lower extremities may be considered to evaluate for deep vein thrombosis.</td>
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<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
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<tr>
<td></td>
<td>Acute exacerbation of chronic obstructive pulmonary disease or underlying malignancy may be at particular risk.[132]</td>
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<tr>
<td></td>
<td>• A low systolic blood pressure and/or the inability to increase the PaO2 to &gt;60 mmHg with oxygen may indicate the presence of a pulmonary embolism.</td>
<td></td>
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<tr>
<td>Pulmonary hypertension</td>
<td>• People with pulmonary hypertension of various etiologies typically experience dyspnea and may have hypoxemia.[133]</td>
<td>• The presence of pulmonary hypertension may be identified by echocardiogram. A multifaceted evaluation may be needed to determine the cause(s). A right heart catheterization may be needed for diagnosis and to guide optimal management in some cases.</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>• Clinically, may be difficult to distinguish. Chest pain may be more apparent, with radiation down left side. Nausea, jaw pain, and/or diaphoresis may be present.</td>
<td>An electrocardiogram should be performed, especially for patients who may require hospitalization for care of an acute exacerbation of COPD, to identify possible cardiac ischemia and arrhythmias.[1]</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>• Differentiating features may include palpitations, lightheadedness, loss of consciousness, and/or collapse.</td>
<td>An electrocardiogram should be performed, especially for patients who may require hospitalization for care of an acute exacerbation of COPD or who are experiencing palpitations or dizziness, to identify possible cardiac ischemia and arrhythmias.[1]</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>• Large airway obstruction typically presents with dyspnea and wheeze (particularly during exertion and with forced exhalation maneuver), and it is commonly mistaken for refractory exacerbations of COPD; variable intrathoracic upper airway obstruction is often caused by</td>
<td>Spirometry with flow volume loop can identify the presence of upper airway obstruction; when tracheobronchomalacia is suspected, CT scanning with inspiration and expiration views or direct bronchoscopic airway inspection can be diagnostic. Ear, nose, and</td>
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</table>

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### Acute exacerbation of chronic obstructive pulmonary disease

#### Diagnosis

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<tbody>
<tr>
<td>tracheobronchomalacia, an aspirated object, or central airway tumor; variable extrathoracic upper airway obstruction is commonly caused by vocal cord paralysis, as well as by inflammation and swelling of the perilaryngeal soft tissues and intermittent vocal cord spasm associated with GERD, undiagnosed or untreated obstructive sleep apnea, and chronic post nasal drip; fixed upper airway obstruction may be caused by tracheal stenosis (e.g., due to prior intubation for mechanical ventilation), extrinsic compression of central airways (e.g., lymphadenopathy or mass), or large airway tumor. Auscultation over the larynx, trachea, and main bronchi during both quiet breathing and forced exhalation or hyperpnea maneuver should be done to evaluate for the presence of upper airway obstruction; complete resolution of wheezing during resting quiet breathing that is present during exertion or a forced exhalation maneuver argues against the presence of bronchoconstriction related to COPD exacerbation.</td>
<td>throat evaluation may be considered for inspection of the vocal cords and perilaryngeal soft tissues.</td>
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#### Excessive oxygen therapy

- While oxygen therapy is clearly indicated for many patients with COPD and acute exacerbations (and should be titrated to achieve an oxygen saturation of 88%-92%), excessive oxygen leads to further degradation of the patient’s respiratory physiology. Exposure to oxygen leads to decrease of hypoxic vasoconstriction of arteries supplying poorly ventilated spaces, increasing the degree of V/Q mismatch.  

- An ABG should be performed for patients who are hypoxemic or are receiving oxygen therapy who present with an apparent acute exacerbation of COPD.
Criteria

Global Initiative for Chronic Obstructive Lung Disease classification of severity of airflow limitation and assessment of exacerbation risk[1]

In pulmonary function testing, a postbronchodilator FEV1/FVC ratio of <0.70 is commonly considered diagnostic for COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) system categorizes airflow limitation into stages.

In patients with FEV1/FVC <0.70:

- GOLD 1 - mild: FEV1 ≥80% predicted
- GOLD 2 - moderate: 50% ≤ FEV1 <80% predicted
- GOLD 3 - severe: 30% ≤ FEV1 <50% predicted
- GOLD 4 - very severe: FEV1 <30% predicted.

The GOLD guideline uses a combined COPD assessment approach to group patients according to symptoms and previous history of exacerbations. Symptoms are assessed using the Modified British Medical Research Council (mMRC) or COPD assessment test (CAT) scale. GOLD cautions against the use of the mMRC dyspnea scale alone for assessing patients, as symptoms of COPD go beyond dyspnea alone. For this reason, the CAT is preferred. However, GOLD acknowledges that the use of the mMRC scale is widespread, and so a threshold of an mMRC grade ≥2 is still included to define "more breathless" patients in its assessment criteria.[1]

- Group A: low risk (0-1 exacerbation per year, not requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT <10)
- Group B: low risk (0-1 exacerbation per year, not requiring hospitalization) and more symptoms (mMRC ≥2 or CAT ≥10)
- Group C: high risk (≥2 exacerbations per year, or one or more requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT <10)
- Group D: high risk (≥2 exacerbations per year, or one or more requiring hospitalization) and more symptoms (mMRC ≥2 or CAT ≥10).

GOLD classification of exacerbation severity:[1]
Acute exacerbation of chronic obstructive pulmonary disease

**Diagnosis**

- **Mild:** requires treatment with short-acting bronchodilators only
- **Moderate:** requires treatment with short-acting bronchodilators plus antibiotics and/or oral corticosteroids
- **Severe:** patient requires hospital admission or visit to the emergency room. Acute respiratory failure may also occur in severe exacerbation.

**GOLD classification of hospitalized patients with acute exacerbations of COPD:**[1]

**No respiratory failure**

- Respiratory rate 20 to 30 breaths/minute
- No use of accessory muscles of respiration
- No changes in mental status
- Hypoxemia improves when supplemental oxygen is given via Venturi mask at 28% to 35% inspired oxygen (FiO2)
- Partial pressure of carbon dioxide (PaCO2) is not increased.

**Acute respiratory failure - nonlife threatening**

- Respiratory rate >30 breaths/minute
- Using accessory muscles of respiration
- No changes in mental status
- Hypoxemia improves when supplemental oxygen is given via Venturi mask at 24% to 35% FiO2
- Hypercarbia occurs: PaCO2 is increased relative to baseline or is elevated (50 mmHg-60 mmHg).

**Acute respiratory failure - life threatening**

- Respiratory rate >30 breaths/minute
- Using accessory muscles of respiration
- Acute changes in mental status
- Hypoxemia does not improve when supplemental oxygen is given via Venturi mask, or FiO2 >40% is required
- Hypercarbia occurs: PaCO2 is increased relative to baseline or is elevated (>60 mmHg), or acidosis is present (pH ≤7.25).
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**Approach**

For updates on diagnosis and management of coexisting conditions during the COVID-19 pandemic, see our topic 'Management of coexisting conditions in the context of COVID-19'.

The overall goals of therapy are to alleviate the patient's symptoms of dyspnea, to stabilize and improve respiratory status, and where possible, to remove the ongoing trigger. Many patients with an acute exacerbation of COPD are stable enough to be managed in the outpatient setting. Key pharmacologic therapies include short-acting bronchodilators, systemic corticosteroids, and antibiotics. Oxygen may also be needed. Patients with more severe exacerbations may need to be admitted to hospital and may require ventilatory support.[1]

The World Health Organization has specified a minimum set of interventions for the management of exacerbations of COPD.[139]

**Treatment setting**

COPD patients and their exacerbations are highly heterogeneous. Some patients with mild exacerbations may be able to manage their symptoms at home using their self-management plan. While many aspects of care are amenable to protocols, those who may require hospitalization, those who may benefit from pulmonary rehabilitation, or those who have a less versus more severe acute exacerbation, will vary according to the comorbidities and other characteristics of each patient.

Hospitalization should be considered for people with:[1]

- Sudden worsening of resting dyspnea
- High respiratory rate (>30 breaths/minute)
- Acute respiratory failure
- Decreased oxygen saturation (SaO₂): SaO₂ <90% on air or deteriorating SaO₂ in patients with known hypoxemia (i.e., those on long-term oxygen therapy)[138]
- Confusion or drowsiness
- Change in or onset of new signs, such as cyanosis or worsening peripheral edema
- Failure to respond to initial management
- Serious comorbidities that would affect recovery or impact treatment, such as heart failure, atrial fibrillation, or other cardiorespiratory conditions
- Insufficient support at home or in the community treatment setting.

The patient should be reassessed if their condition worsens rapidly or significantly. In particular, physicians should be alert for symptoms and signs of pneumonia, cardiorespiratory failure, and sepsis.[140]

Patients who meet any of the following criteria require immediate admission to the intensive care unit (ICU), or a respiratory care unit that is equipped to identify and manage acute respiratory failure:[1]

- Severe dyspnea that does not respond adequately to initial treatment
- Changes in mental status (e.g., confusion, lethargy, coma)
- Hypoxemia that persists or worsens (partial pressure of oxygen [PaO₂] <5.3kPa or <40mmHg) and/or respiratory acidosis that is severe or worsening (pH <7.25), despite supplemental oxygen therapy and noninvasive ventilation
- Invasive mechanical ventilation is needed
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- Hemodynamic instability (vasopressors are needed).

ICU admission should also be considered for those who newly require noninvasive ventilation and/or acute respiratory acidosis; this may depend on local hospital resources and policy.

**Short-acting bronchodilators**

Short-acting bronchodilators include beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs). SABAs and SAMAs both reduce symptoms of dyspnea and also improve airflow, possibly by decreasing lung hyperinflation.[141] These medications are considered first-line therapy, and are delivered either by nebulization or by metered-dose inhaler (MDI).[142] SABAs and SAMAs may provide benefit within 15 and 30 minutes, respectively. Optimal dosing of bronchodilators in acute exacerbations of COPD has not yet been determined; however, guidelines generally recommend increasing the dose or frequency of administration if the patient remains symptomatic. After clinical improvement, the time between doses may be increased as tolerated.

SABAs are typically favored as they have a faster onset of action than SAMAs. International guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend SABAs, with or without SAMAs, as the initial bronchodilators to treat an acute exacerbation of COPD.[1] Initial therapy with SABAs may lead to a transient reduction in PaO2.[145] If the initial dose of SABA does not provide sufficient benefit, the frequency of dosing may be increased and a SAMA may be added.[143] Nebulized ipratropium (a SAMA) may be given in combination with nebulized albuterol (a SABA). Ipratropium may be used in lieu of albuterol for patients developing significant adverse effects due to SABA use. Levalbuterol may also be used in lieu of racemic albuterol, and it may be possible to provide levalbuterol less frequently than racemic albuterol in patients with exacerbations. Levalbuterol may be best considered for patients who have adverse cardiovascular effects from albuterol (e.g., tachycardia/tachyarrhythmia).[147]

It is not clear whether the combination of a SABA plus a SAMA provides additional benefit.[143] While there is no definitive evidence that the combination improves outcomes, patients may derive symptomatic benefit, plus additional bronchodilation, because these agents work by different mechanisms. Combination therapy is generally recommended for patients who are not improving promptly on a SABA alone.[1]

One systematic review did not find significant differences in FEV1 when short-acting bronchodilators were delivered by a nebulizer, compared with an MDI (with or without a spacer device), in patients with an acute exacerbation of COPD.[150] Patients with severe dyspnea and low inspiratory flow rates may have difficulty achieving proper technique and medication delivery with MDIs; nebulizer treatment may be easier to use for such patients. Technique with MDIs should be observed and a spacer should be used.

Guidelines from GOLD recommend that patients do not receive continuous nebulization, but rather, take 1 or 2 puffs every hour from an MDI (plus spacer) for two or three doses, and then every 2 to 4 hours based on response.[1] If a nebulizer is used to deliver the inhaled drugs, then it should be driven by air, not oxygen, in order to avoid the risk of worsening hypercarbia that may be caused by oxygen-driven nebulization.[1] [138]

There are as yet no clinical trials to clearly guide whether or not long-acting bronchodilators should be continued during acute COPD exacerbations. Although discontinuation of a maintenance therapy might potentially contribute to worsening symptoms and/or lung function, regular frequent administration of short-acting bronchodilators, in addition to long-acting bronchodilators of the same class, has the potential
to increase the risk of medication-related adverse effects, such as arrhythmia, urinary retention, and constipation. The current GOLD report recommends continuing inhaled long-acting bronchodilators during an exacerbation, or starting them as soon as possible before discharge from hospital.[1]

Clinical judgement should dictate whether or not to continue long-acting bronchodilators during acute hospitalizations for COPD when patients are receiving short-acting bronchodilators four or more times per day. Consideration should be made as to whether adjustments to pre-hospitalization drug regimens are needed, based on recommendations for step-up therapy to reduce future risk of exacerbations.[1]

**Systemic corticosteroids**

Systemic (oral or intravenous) corticosteroids should be considered after initial treatment with short-acting inhaled bronchodilators.[1] For patients able to take oral medications, intravenous corticosteroids do not appear to provide any significant benefit over those taken orally.[151] [152] [153] [154] However, some patients may require intravenous administration if they cannot tolerate oral therapy (e.g., if they are vomiting).

Systemic corticosteroids decrease airway inflammation and have been shown to be beneficial for patients with acute exacerbations of COPD.[155] [156] [151] [157] [152] They have been associated with greater early (within 3 days) improvement in FEV1, improved oxygenation, faster recovery time, decreased duration of hospitalization, and decreased rate of treatment failure and relapsed disease.[1] [155] [156] [151] [157] However, there is no evidence that the use of corticosteroids has an effect on rates of mortality.[151] In addition, corticosteroids are associated with increased risk of pneumonia, sepsis, and death.[158] They should only be used in patients with significant exacerbations.[1]

Studies examining the role of systemic corticosteroids have been primarily performed among people presenting to emergency rooms and those who are hospitalized, and have used a range of dose amounts and treatment durations.

Previous national and international guidelines recommended that patients receive prednisone, or equivalent, for 7 to 14 days.[137] [143] It is not known whether tapering systemic corticosteroids provides any clinical benefit apart from likely avoidance of adrenal insufficiency. One randomized controlled trial showed that 5 days’ treatment of prednisone was noninferior to 14 days’ treatment with regard to the risk of exacerbations in the subsequent 6 months.[159] One Cochrane systematic review concluded that five days of oral corticosteroids is likely to be sufficient for acute exacerbations of COPD, and that it is unlikely that shorter courses of systemic corticosteroids (of around five days) lead to worse outcomes than longer courses (10 to 14 days).[160] This 5-day regimen is recommended by the GOLD guidelines.[1] The Department of Veterans’ Affairs recommends prednisone for 5 to 7 days.[137] An equivalent oral dose of methylprednisolone may be used. Joint guidelines from the European Respiratory Society and American Thoracic Society recommend a short course (≤14 days) of oral corticosteroids for ambulatory patients with an exacerbation of COPD.[161]

The balance of risks and benefits of corticosteroids for people with milder exacerbations is uncertain. Eosinophil count may prove to be useful in determining who should receive corticosteroids for acute exacerbations of COPD; corticosteroids may be less effective for acute exacerbations of COPD among patients with lower blood eosinophil levels.[162] [163]

The benefit of systemic corticosteroid therapy for people with acute exacerbations of COPD with associated respiratory failure requiring mechanical ventilatory support is also unclear. One randomized controlled trial found no difference in ICU mortality, duration of mechanical ventilation, or ICU length of
stay between patients who received prednisone versus the control group who did not, yet those who received prednisone had a higher risk of hyperglycemia.[164]

The presence of pneumonia as a cause of respiratory decompensation in a patient with COPD does not necessarily imply the presence of a COPD exacerbation per se (i.e., the presence of worsened airflow limitation related to airways inflammation and/or bronchoconstriction), and as such, careful consideration should be given as to whether systemic corticosteroids are warranted in such patients.

Diabetes is common in patients with COPD, and the need for treatment of hyperglycemia is more frequently encountered when patients receive systemic corticosteroids.[156] [151]

Nebulized corticosteroids have been used with some success, but their utility in acute exacerbations of COPD and relative efficacy compared with systemic corticosteroids is not fully clear.[165] Nebulized budesonide may be suitable in some patients, providing similar clinical outcomes to intravenous methylprednisolone, although local costs and availability may vary.[1] [166]

Corticosteroids may pose a risk of development and/or worsening of tracheobronchomalacia, which may mimic COPD exacerbations.[167]

**Airway clearance techniques**

Selected airway clearance techniques, such as mechanical vibration and nonoscillating positive expiratory pressure devices, may improve sputum clearance in some patients with copious secretions, or concurrent bronchiectasis, and may slightly reduce short-term risk of need for ventilatory assistance.[168] However, they are not uniformly helpful.[169] Other clearance techniques, such as manual chest wall percussion, are also either not routinely helpful or may have detrimental effects.[170] [171] [172] There is as yet no proven benefit of airway clearance techniques on long-term outcomes following COPD exacerbation, such as reduction in subsequent exacerbation risk.[168]

**Oxygen**

Oxygen therapy is recommended for patients with acute exacerbations who are hypoxemic (PaO2 <60 mmHg, oxygen saturation <90%). Oxygen should be applied with caution to prevent further hypercarbia. Arterial blood gas and pulse oximetry should be checked on presentation, and then after 30 to 60 minutes, to ensure satisfactory oxygenation and to check for carbon dioxide retention and/or respiratory acidosis.[1] [122] Controlled oxygen should be titrated to a target saturation of 88% to 92% as COPD patients are considered at risk for hypercarbic (type 2) respiratory failure.[1] [122] Careful titration of supplemental oxygen, even in the prehospital setting (e.g., en route to the hospital), is important to prevent worsening respiratory acidosis, which may increase mortality.[173]

Oxygen is best administered in a controlled fashion via a high-flow Venturi mask to deliver 24% to 28% oxygen.[122]

Excessive oxygen therapy may lead to worsening hypercarbia, acidosis, and respiratory failure, due to worsening V/Q mismatch and decreased CO2-carrying capacity of oxygenated erythrocytes (Haldane effect). For this reason, oxygen delivery via a high-flow Venturi mask is favored over nasal prongs, as nasal prongs are less accurate and deliver higher inspired oxygen concentrations.[1] [174] High-flow oxygen (HFO) therapy may be an alternative to standard oxygen therapy or noninvasive mechanical ventilation in patients with acute hypoxemic respiratory failure.[1] HFO involves the delivery of heated, humidified oxygen at up to 60 L/min in adults via special nasal cannulae.[175] However, there is currently
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insufficient evidence to recommend the use of HFO in acute hypoxemic/hypercarbic respiratory failure in patients with COPD.[1]

Oxygen therapy may be discontinued when the patient is able to maintain their target oxygen saturation on room air.[122] Oxygen saturation should be checked at rest, with exertion, and during sleep (if possible) prior to discharge for hospitalized patients, in order to determine if supplemental oxygen will be newly needed in the home, or if changes to prior oxygen prescription are necessary.

Other drugs

While methylxanthine medications, such as theophylline or aminophylline, may provide benefit to some people with COPD, this class of medications has a narrow therapeutic window and there does not appear to be a role for use in patients with acute exacerbations of COPD.[1] [167] [177] [178]

The use of mucolytics, expectorants, and/or physical mucus-clearing techniques does not appear to provide any clear proven benefit during exacerbations, although some patients do experience symptomatic relief.[169] [142]

Exacerbations with suspected bacterial etiology

Bacterial infections are thought to be a common trigger of exacerbations.[75] Interactions between host factors, bacteria, viruses, and changes in air quality are also thought to cause, or contribute toward, exacerbations.[1] [71] Many exacerbations are not caused by bacterial infections, so will not respond to antibiotics.[140]

Multiple, randomized placebo-controlled trials have shown that antibiotics are beneficial for the treatment of patients with acute exacerbations of COPD.[76] [179] [180] However, one updated Cochrane review concluded that the effects of antibiotics for non-ICU patients are small, are inconsistent for some outcomes (treatment failure), and absent for other outcomes (mortality and length of hospital stay).[181] When this Cochrane review restricted its analysis to four studies that assessed the currently used antibiotics of non-ICU inpatients, a beneficial effect in terms of treatment failure was found but it was not statistically significant (risk ratio 0.65, 95% CI 0.38 to 1.12).[181] For outpatients, currently used antibiotics statistically significantly reduced the risk for treatment failure (risk ratio 0.72, 95% CI 0.56 to 0.94).[181]

International guidelines from GOLD recommend antibiotics for people with acute exacerbations of COPD and:

- increased sputum purulence, plus
- increased sputum volume, and/or
- increased dyspnea.

Some patients with COPD may keep antibiotics at home for use in an exacerbation as part of their self-management plan.[140]

Patients with more severe exacerbations, particularly those requiring treatment in the ICU, have been shown to derive greater benefit from antibiotic therapy.[181] [76] International guidelines from GOLD recommend that antibiotics should be given to patients with severe exacerbations requiring mechanical ventilation (invasive or noninvasive).[1]

Patients who receive antibiotics are at increased risk for antibiotic-associated diarrhea, compared with placebo, although the difference is not statistically significant.[181]
Management

Antibiotic choice and duration of therapy is an unresolved issue, but in general should be based on local resistance patterns and patient characteristics, including any previous culture results for the patient.[1] [137] The most common bacterial pathogens include: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. [32] [37]

It has been shown that short courses of antibiotics (e.g., 5 days) are equally effective as longer courses (e.g., >5 days) for patients with mild to moderate exacerbations of COPD.[182] [183] [184] When indicated, GOLD recommends that the duration of antibiotic therapy should be 5 to 7 days, but local guidelines should be consulted.[1]

Oral antibiotics should be given first-line if possible, and if the severity of the exacerbation does not necessitate intravenous antibiotics.[1] [140] If the patient’s dyspnea and/or sputum purulence improve, this suggests that the antibiotic is effective.[1] Guidelines from the National Institute for Health and Care Excellence (NICE) recommend that, if intravenous antibiotics are given, they should be reviewed within 48 hours and stepped down to oral antibiotics where possible.[140] Antibiotic-resistant bacteria should be considered, and a sputum sample sent for microscopy, culture, and Gram stain if symptoms have not improved following antibiotic treatment, and if these tests have not been done already.[140]

It has been recommended that more narrow-spectrum antibiotics (e.g., amoxicillin, amoxicillin/clavulanate, doxycycline, second-generation cephalosporins, macrolides, trimethoprim/sulfamethoxazole) be considered for patients at less risk for a poor outcome and with an exacerbation of lesser severity.[137] The severity depends on the patient’s prior status and any changes to previous baseline investigation (based on symptoms, examination, lung function, ABG).

Patients with more severe underlying COPD, and those with greater exacerbation severity, are more often colonized with gram-negative bacteria such as *Pseudomonas aeruginosa* or other enteric gram-negative organisms and/or *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus*).[74] [37] Therefore, broad-spectrum antibiotics such as ampicillin/sulbactam, piperacillin/tazobactam, vancomycin, and fluoroquinolones are considered for patients at greater risk for a poor outcome, or with an episode of greater severity.[74] [137] Agents with activity against *Pseudomonas aeruginosa* are also indicated for people at risk of this infection.[37] The choice of antibiotic should also be based in part on local bacterial resistance patterns.

Sputum cultures or endotracheal aspirates (in patients who are intubated) are recommended for assessment of bacterial infection in patients with severe lung function impairment, those with a history of frequent exacerbations, and/or in patients hospitalized with COPD exacerbations or who require mechanical ventilation, as gram-negative bacteria (such as *Pseudomonas* species) or resistant pathogens may be present.[1] [37] Consideration may also be given to obtaining a sputum culture in patients who have bronchiectasis and suspected infectious exacerbations as a feature of their COPD.

Risk factors for a poor outcome include recent history of antibiotic use, more severe baseline COPD, need for hospitalization, treatment failure, prior antibiotic resistance, or risk factors for healthcare-associated infections. Critically ill patients in the ICU are also at higher risk.[137] [137]

Use of accessory muscles of respiration, paradoxical respirations, cyanosis, new peripheral edema, hemodynamic instability, and worsened mental status (e.g., confusion, lethargy, coma) are important indicators of a more severe exacerbation.[1]

Specialist advice may be needed if symptoms do not improve after repeated courses of antibiotics, or with a bacterial infection resistant to oral antibiotics, or for patients who cannot take oral medications.[140]
Studies have suggested that the use of a respiratory fluoroquinolone, amoxicillin/clavulanate, second- or third-generation cephalosporins, or macrolides may be associated with fewer treatment failures or recurrent exacerbations.[185] [186] [187] [188] [189] [190] One meta-analysis of randomized controlled trials found that there were no differences between patients with acute exacerbation of chronic bronchitis receiving semisynthetic penicillins (e.g., amoxicillin, ampicillin), and those receiving trimethoprim-based regimens (e.g., trimethoprim, trimethoprim/sulfamethoxazole), in terms of treatment success and number of drug-related adverse events in general.[191] One randomized controlled trial has shown that three months of azithromycin for an infectious exacerbation of COPD that requires hospitalization may reduce treatment failure during the highest-risk period.[192]

In November 2018, the European Medicines Agency (EMA) completed a review of serious, disabling, and potentially irreversible adverse effects associated with systemic and inhaled fluoroquinolone antibiotics. These adverse effects include tendonitis, tendon rupture, arthralgia, neuropathies, and other musculoskeletal or nervous system effects. As a consequence of this review, the EMA now recommends that fluoroquinolone antibiotics be restricted for use in serious, life-threatening bacterial infections only. Furthermore, they recommend that fluoroquinolones should not be used for mild to moderate infections, unless other appropriate antibiotics for the specific infection cannot be used, and should not be used in nonsevere, nonbacterial, or self-limiting infections. Patients who are older, have renal impairment, or have had a solid organ transplant, and those being treated with a corticosteroid, are at a higher risk of tendon damage. Co-administration of a fluoroquinolone and a corticosteroid should be avoided where possible.[193] The UK-based Medicines and Healthcare products Regulatory Agency (MHRA) support these recommendations.[194] The Food and Drug Administration (FDA) issued a similar safety communication in 2016, restricting the use of fluoroquinolones in acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.[195] In addition to these restrictions, the FDA has issued warnings about the increased risk of aortic dissection, significant hypoglycemia, and mental health adverse effects in patients taking fluoroquinolones.[196] [197] Therefore, fluoroquinolones should be used only when it is considered inappropriate, or when it is impossible to use other antibacterial agents that are commonly recommended for the treatment of these infections.

There is currently insufficient evidence to guide use of antibiotics based on serum procalcitonin levels in patients with COPD.[1] Importantly, procalcitonin-guided antibiotic use is not recommended for COPD exacerbations in the ICU setting, as this has been associated with increased mortality.[113] C-reactive protein (CRP) is also being investigated as a potential biomarker to guide the use of antibiotics during exacerbations of COPD. A decision to withhold antibiotics based on low CRP levels at the point of care has been associated with reduced antibiotic prescriptions, without worse clinical outcomes.[114] [115] [116]

**Ventilatory support**

Respiratory failure is often seen in patients with severe acute exacerbations of COPD. Patients with severe exacerbations who do not appear to respond sufficiently to initial interventions should be considered for noninvasive mechanical ventilation (NIV). The use of NIV has been shown to improve gas exchange, reduce dyspnea, decrease the need for endotracheal intubation, reduce complications such as pneumonia, and decrease length of hospitalization and mortality in these patients.[1] [109] [198] [199] [200] [201] [202] Where possible, NIV should be used in preference to invasive mechanical ventilation for respiratory failure associated with COPD exacerbation.

NIV use should be considered for patients with one or more of the following:[1]
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- Respiratory acidosis (partial pressure of carbon dioxide [PaCO2] ≥6.0 kPa or 45 mmHg and arterial pH ≤7.35)
- Severe dyspnea with signs that suggest fatigue of respiratory muscles, or increased work or breathing, or both, such as the use of accessory muscles of respiration, paradoxical movement of the abdomen, or retraction of the intercostal spaces
- Persistent hypoxemia while on supplemental oxygen.

Improvements in patients' level of dyspnea and their physiologic state are typically seen within 1 to 4 hours.[203] The GOLD report recommends that if patients improve, and can breathe unassisted for at least 4 hours, then NIV can be stopped.[1]

However, NIV is not successful for all patients. Clinicians should discuss the risks and benefits of invasive mechanical ventilation with patients receiving NIV to determine their desired course of treatment.

Invasive mechanical ventilation should be considered for patients with outright respiratory or cardiac arrest, who are in, or have signs of, impending acute respiratory failure despite NIV, have impaired mental status or cardiovascular instability, are at high risk for aspiration, or for whom NIV cannot be appropriately applied (e.g., craniofacial trauma, recent gastroesophageal surgery, copious secretions, anxiety disorder, facial discomfort, or severe skin breakdown).[204]

Physiologic criteria for invasive mechanical ventilation include the following: life-threatening hypoxemia in patients unable to tolerate NIV, inability to tolerate NIV or failure of NIV, respiratory or cardiac arrest, irregular breathing with gasping or loss of consciousness, massive aspiration or persistent vomiting, inability to clear respiratory secretions, heart rate <50 beats per minute with diminished alertness, severe hemodynamic instability not responsive to medical treatment, or severe ventricular or supraventricular arrhythmias.[1] [205]

The risk for mortality is significant (11% to 49%) for people with severe disease in whom invasive mechanical ventilation is indicated.[12] [206] Complications of mechanical ventilation include ventilator-associated pneumonia and barotrauma. Weaning patients with severe COPD from mechanical ventilation can be difficult.[204] Use of NIV to assist weaning from mechanical ventilation can reduce weaning failure and nosocomial pneumonia, and may reduce mortality.[207] [208]

Other considerations

Depending on the patient's clinical condition, the following may also need to be addressed:[1]

- Monitoring and correction of fluid balance (e.g., in patients with heart failure)
- Treatment of any comorbidities (e.g., lung cancer, cardiovascular disease, osteoporosis, depression)
- Thromboprophylaxis
- Nutritional supplements
- Smoking cessation (e.g., nicotine replacement therapy).

Pulmonary rehabilitation and disease management programs

Patients with COPD who experience acute exacerbations of COPD often have skeletal muscle dysfunction (potentially due to limited physical activity), nutritional disturbances, corticosteroid use, and/or systemic inflammatory factors.[212] [213]
Pulmonary rehabilitation is a multidisciplinary program of care that involves physical rehabilitation as well as guidance on disease management, nutrition, and other lifestyle issues (e.g., smoking cessation, medication adherence and inhaler technique, supplemental oxygen, and maintenance of physical activity).[214] [215] As COPD patients and their exacerbations are highly heterogeneous, determining who may benefit from respiratory rehabilitation varies greatly according to the comorbidities and other characteristics of individual patients.

- Selected forms of exercise rehabilitation initiated during a hospitalization for COPD exacerbation, including resistance strength training and transcutaneous electrical muscle stimulation, are well tolerated and can prevent muscle function decline and hasten functional status recovery.[216] [217] [218]
- Pulmonary rehabilitation initiated early during the recovery phase of an exacerbation is safe and effective, and leads to improvements in exercise tolerance, physical abilities, the degree of symptoms due to COPD, and quality of life.[219] [220] [221] [222] [223] [224] [225] [226]
- Comprehensive supervised pulmonary rehabilitation in the outpatient setting in the post-exacerbation period decreases the risk for future hospitalization.[215] [222] [223] [227] Participation in pulmonary rehabilitation within 90 days of discharge following hospitalization for COPD exacerbation is associated with a significant decrease in mortality risk.[228] Unsupervised, home-based exercise training following exacerbations does not appear to confer the same benefits.[229]

Disease management programs can be helpful. However, their use remains controversial given that a randomized controlled trial had to be stopped early due to a noted increase in mortality in the comprehensive care management group, compared with the control patients who were receiving guideline-based routine medical care.[214] [230] [231] [232] [233] Another study involving unsupervised home-based exercise training following hospitalization for acute COPD exacerbation also showed a mortality signal at the 6-month, post-hospitalization time point.[229]

Some data are emerging that hospital-at-home care, with support from respiratory nurses, may be appropriate for selected people with moderate exacerbations of COPD.[234] However, this approach is not yet considered the standard of care, and people with unstable vital signs, decompensated gas exchange, acute respiratory acidosis, worsened hypoxemia, change in mental status, or significant comorbid illness are not suitable for this approach.[95] [235]

A randomized controlled trial has suggested that the use of nurse-centered tele-assistance may decrease the occurrence of exacerbations of COPD and hospitalization. The use of such programs may be cost-saving.[236] However, another randomized controlled trial demonstrated that tele-monitoring integrated into existing clinical services did not reduce hospital admissions or improve patients’ quality of life.[237]

**Treatment algorithm overview**

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer
## Acute exacerbation of chronic obstructive pulmonary disease

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#### Acute

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<td>suspected bacterial etiology (exacerbation of greater severity)</td>
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<td>respiratory insufficiency</td>
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Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: [see disclaimer](#).
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Management

**Acute at presentation**

1st short-acting bronchodilator

**Primary options**

- **albuterol inhaled**: consult specialist for guidance on dose
- **levalbuterol inhaled**: consult specialist for guidance on dose
--AND/OR--
- **ipratropium bromide inhaled**: consult specialist for guidance on dose

Short-acting bronchodilators include short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs). These medications are considered first-line therapy and are delivered either by nebulization or by metered-dose inhaler. SABAs and SAMAs may provide benefit within 15 and 30 minutes, respectively. Optimal dosing of bronchodilators in acute exacerbations of COPD has not yet been determined; however, guidelines generally recommend increasing the dose or frequency of administration if the patient remains symptomatic. After clinical improvement, the time between doses may be increased as tolerated.

SABAs are typically favored as they have a faster onset of action than SAMAs. International guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend SABAs, with or without SAMAs, as the initial bronchodilators to treat an acute exacerbation of COPD. Initial therapy with SABAs may lead to a transient reduction in partial pressure of oxygen (PaO2). If the initial dose of SABA does not provide sufficient benefit, the frequency of dosing may be increased and a SAMA may be added. Nebulized ipratropium (a SAMA) may be given in combination with nebulized albuterol (a SABA). Ipratropium may be used in lieu of albuterol for patients developing significant adverse effects due to SABA use. Levalbuterol may be used in lieu of racemic albuterol and it may be possible to provide levalbuterol less frequently than racemic albuterol in patients with exacerbations. Levalbuterol may be best considered for patients who have adverse cardiovascular effects from albuterol (e.g., tachycardia/ tachyarrhythmia).
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It is not clear whether the combination of a SABA plus a SAMA provides additional benefit. While there is no definitive evidence that the combination improves outcomes, patients may derive symptomatic benefit, plus additional bronchodilation, because these agents work by different mechanisms. Combination therapy is generally recommended for patients who are not improving promptly on a SABA alone.

One systematic review did not find significant differences in FEV1 when short-acting bronchodilators were delivered by a nebulizer, compared with an MDI (with or without a spacer device), in patients with an acute exacerbation of COPD. Patients with severe dyspnea and low inspiratory flow rates may have difficulty achieving proper technique and medication delivery with MDIs; nebulizer treatment may be easier to use for such patients. Technique with MDIs should be observed and a spacer should be used.

Guidelines from GOLD recommend that patients do not receive continuous nebulization, but rather, take 1 or 2 puffs every hour from an MDI (plus spacer) for two or three doses, and then every 2 to 4 hours based on response. If a nebulizer is used to deliver the inhaled drugs, then it should be driven by air, not oxygen, in order to avoid the risk of worsening hypercarbia that may be caused by oxygen-driven nebulization.

There is insufficient evidence to determine whether MDIs or the aerosol nebulizer technique is the optimal method of delivering bronchodilators to adults with COPD exacerbations who are receiving mechanical ventilation via endotracheal tube.

There are as yet no clinical trials to clearly guide whether or not long-acting bronchodilators should be continued during acute COPD exacerbations. Although discontinuation of a maintenance therapy might potentially contribute to worsening symptoms and/or lung function, regular frequent administration of short-acting bronchodilators, in addition to long-acting bronchodilators of the same class, has the potential to increase the risk of medication-related adverse effects, such as arrhythmia, urinary retention, and constipation. The current GOLD report recommends continuing inhaled long-acting bronchodilators during an exacerbation, or starting them as soon as possible before discharge from hospital.
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Clinical judgement should dictate whether or not to continue long-acting bronchodilators during acute hospitalizations for COPD when patients are receiving short-acting bronchodilators four or more times per day. Consideration should be made as to whether adjustments to pre-hospitalization drug regimens are needed, based on recommendations for step-up therapy to reduce future risk of exacerbations.[1]

- Optimal dosing of bronchodilators in acute exacerbations of COPD has not been established. Adjust dose according to clinical symptoms and adverse effects. Higher or more frequent dosing may be required.

**adjunct systemic corticosteroid**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **prednisone**: 30-40 mg orally once daily

  OR

- **methylprednisolone**: 40-60 mg/day orally given once daily or in 2 divided doses

  OR

- **methylprednisolone sodium succinate**: 0.5 to 2 mg/kg intravenously every 6 hours for up to 72 hours, followed by taper or change to oral dosing

**Systemic (oral or intravenous) corticosteroids should be considered after initial treatment with short-acting inhaled bronchodilators.[1] For patients able to take oral medications, intravenous corticosteroids do not appear to provide any significant benefit over those taken orally.[151] [152] [153] [154] However, some patients may require intravenous administration if they cannot tolerate oral therapy (e.g., if they are vomiting).

**Systemic corticosteroids have been associated with greater early (within 3 days) improvement in FEV1, improved oxygenation, faster recovery time, decreased duration of hospitalization, and decreased rate of treatment failure and relapsed disease.[1] [155] [156] [151] [157] [152] However, there is no evidence that the use of corticosteroids has an effect on rates of mortality.[151] In addition, corticosteroids are associated with increased...**
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risk of pneumonia, sepsis, and death.\[158\] They should only be used in patients with significant exacerbations.\[1\]

» Previous national and international guidelines recommended that patients receive prednisone, or equivalent, for 7 to 14 days.\[137\] \[143\] It is not known whether tapering systemic corticosteroids provides any clinical benefit apart from likely avoidance of adrenal insufficiency. One randomized controlled trial showed that 5 days’ treatment of prednisone was noninferior to 14 days’ treatment with regard to the risk of exacerbations in the subsequent 6 months.\[159\] One Cochrane systematic review concluded that five days of oral corticosteroids is likely to be sufficient for acute exacerbations of COPD, and that it is unlikely that shorter courses of systemic corticosteroids (of around five days) lead to worse outcomes than longer courses (10 to 14 days).\[160\] This 5-day regimen is recommended by the Global Initiative for Chronic Obstructive Lung Disease guidelines.\[1\] The Department of Veterans’ Affairs recommends prednisone for 5 to 7 days.\[137\] An equivalent oral dose of methylprednisolone may be used. Joint guidelines from the European Respiratory Society and American Thoracic Society recommend a short course (≤14 days) of oral corticosteroids for ambulatory patients with an exacerbation of COPD.\[161\]

» One systematic review found no difference in risk of treatment failure or relapse, likelihood of an adverse event, length of hospital stay, or lung function, at the end of short (approximately 5 days) and longer (10-14 days) courses of systemic corticosteroids.\[151\]

» The balance of risks and benefits of corticosteroids for people with milder exacerbations is uncertain.

» The benefit of systemic corticosteroid therapy for people with acute exacerbations of COPD with associated respiratory failure requiring mechanical ventilatory support is also unclear. One randomized controlled trial found no difference in intensive care unit (ICU) mortality, duration of mechanical ventilation, or ICU length of stay between patients who received prednisone versus the control group who did not, yet those who received prednisone had a higher risk of hyperglycemia.\[164\]

» The presence of pneumonia as a cause of respiratory decompensation in a patient with COPD does not necessarily imply
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|------------------|---------------------------------------------------|
| **Acute**        | the presence of a COPD exacerbation per se (i.e., the presence of worsened airflow limitation related to airways inflammation and/or bronchoconstriction), and as such, careful consideration should be given as to whether systemic corticosteroids are warranted in such patients. |

» Diabetes is common in patients with COPD, and the need for treatment of hyperglycemia is more frequently encountered when patients receive systemic corticosteroids.[156][151]

<table>
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<th>Adjunct</th>
<th>airway clearance techniques</th>
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<td>Treatment recommended for SOME patients in selected patient group</td>
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> Selected airway clearance techniques, such as mechanical vibration and nonoscillating positive expiratory pressure devices, may improve sputum clearance in some patients with copious secretions, or concurrent bronchiectasis, and may slightly reduce short-term risk of need for ventilatory assistance.[168] However, they are not uniformly helpful.[169] Other clearance techniques, such as manual chest wall percussion, are also either not routinely helpful or may have detrimental effects.[170][171][172] There is as yet no proven benefit of airway clearance techniques on long-term outcomes following COPD exacerbation, such as reduction in subsequent exacerbation risk.[168]

<table>
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<th>Adjunct</th>
<th>oxygen</th>
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> Oxygen therapy is recommended for patients with acute exacerbations who are hypoxemic (partial pressure of oxygen [PaO2] <60 mmHg, oxygen saturation [SaO2] <90%). Oxygen should be applied with caution to prevent further hypercarbia. Arterial blood gas and pulse oximetry should be checked on presentation, and then after 30 to 60 minutes, to ensure satisfactory oxygenation and to check for carbon dioxide retention and/or respiratory acidosis.[1][122] Controlled oxygen should be titrated to a target saturation of 88% to 92% as COPD patients are considered at risk for hypercarbic (type 2) respiratory failure.[1][122] Careful titration of supplemental oxygen, even in the prehospital setting (e.g., en route to the hospital), is important to prevent worsening respiratory acidosis, which may increase mortality.[173]
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» Oxygen is best administered in a controlled fashion via a high-flow Venturi mask to deliver 24% to 28% oxygen.[122]

» Excessive oxygen therapy may lead to worsening hypercarbia, acidosis, and respiratory failure, due to worsening V/Q mismatch and decreased CO2-carrying capacity of oxygenated erythrocytes (Haldane effect). For this reason, oxygen delivery via a high-flow Venturi mask is favored over nasal prongs, as nasal prongs are less accurate and deliver higher inspired oxygen concentrations.[1] Nasally-delivered high-flow oxygen may be a suitable alternative to noninvasive mechanical ventilation for some patients with severe COPD exacerbations in the intensive care unit setting.[1]

» Oxygen therapy may be discontinued when the patient is able to maintain their target oxygen saturation on room air.[122] Oxygen saturation should be checked at rest, with exertion, and during sleep (if possible) prior to discharge for hospitalized patients, in order to determine if supplemental oxygen will be newly needed in the home, or if changes to prior oxygen prescription are necessary.

adjunct support care

Treatment recommended for SOME patients in selected patient group

» Depending on the patient’s clinical condition, the following may also need to be addressed: monitoring and correction of fluid balance (e.g., in patients with heart failure); treatment of any comorbidities (e.g., lung cancer, cardiovascular disease, osteoporosis, depression); thromboprophylaxis; nutritional supplements; smoking cessation (e.g., nicotine replacement therapy).[1]

suspected bacterial etiology (exacerbation of lesser severity)

adjunct narrow-spectrum antibiotic

Treatment recommended for SOME patients in selected patient group

Primary options

» amoxicillin: 500 mg orally three times daily

OR

» doxycycline: 100 mg orally twice daily

OR
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- **sulfamethoxazole/trimethoprim**: 160 mg orally twice daily  
  Dose refers to trimethoprim component.

  **OR**

- **azithromycin**: 500 mg orally once daily on day 1, followed by 250 mg once daily for 4 days

**Secondary options**

- **cefuroxime axetil**: 250-500 mg orally twice daily

  **OR**

- **amoxicillin/clavulanate**: 875 mg orally twice daily  
  Dose refers to amoxicillin component.

  **OR**

- **clarithromycin**: 500 mg orally twice daily

International guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend antibiotics for people with acute exacerbations of COPD and an increase in sputum purulence, plus an increase in sputum volume, and/or increased dyspnea.\(^1\)

It has been recommended that more narrow-spectrum antibiotics (e.g., amoxicillin, amoxicillin/clavulanate, doxycycline, second-generation cephalosporins, macrolides, trimethoprim/sulfamethoxazole) be considered for patients at less risk for a poor outcome and with an exacerbation of lesser severity.\(^{137}\) The severity depends on the patient's prior status and any changes to previous baseline investigation (based on symptoms, examination, lung function, ABG).\(^{140}\)

Some patients with COPD may keep antibiotics at home for use in an exacerbation as part of their self-management plan.\(^{140}\)

Patients who receive antibiotics are at increased risk for antibiotic-associated diarrhea, compared with placebo, although the difference is not statistically significant.\(^{181}\)

Antibiotic choice and duration of therapy is an unresolved issue, but in general should be based on local resistance patterns and patient characteristics, including any previous...
### Acute exacerbation of chronic obstructive pulmonary disease

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The most common bacterial pathogens include: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. [32][37]

» It has been shown that short courses of antibiotics (e.g., 5 days) are equally effective as longer courses (e.g., >5 days) for patients with mild to moderate exacerbations of COPD. [182][183][184] When indicated, GOLD recommends that the duration of antibiotic therapy should be 5 to 7 days, but local guidelines should be consulted. [1]

» Oral antibiotics should be given first-line if possible, and if the severity of the exacerbation does not necessitate intravenous antibiotics. [1][140] If the patient’s dyspnea and/or sputum purulence improve, this suggests that the antibiotic is effective. [1]

» Antibiotic-resistant bacteria should be considered, and a sputum sample sent for microscopy, culture, and Gram stain if symptoms have not improved following antibiotic treatment, and if these tests have not been done already. [140]

» Specialist advice may be needed if symptoms do not improve after repeated courses of antibiotics, or with a bacterial infection resistant to oral antibiotics, or for patients who cannot take oral medications. [140]

**suspected bacterial etiology (exacerbation of greater severity)**

adjunct **broad-spectrum antibiotic**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **ampicillin/sulbactam**: 1.5 to 3 g intravenously every 6 hours
  The 1.5 g dose consists of 1 g of ampicillin and 0.5 g of sulbactam; the 3 g dose consists of 2 g of ampicillin and 1 g of sulbactam.

  **OR**

- **piperacillin/tazobactam**: 3.375 g intravenously every 6 hours
  Dose consists of 3 g of piperacillin and 0.375 g of tazobactam.
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- **vancomycin**: 500-1000 mg intravenously every 12 hours

### Secondary options

- **levofloxacin**: 500 mg orally/intravenously once daily
  
  OR
  
  - **ciprofloxacin**: 500-750 mg orally twice daily; 400 mg intravenously every 8-12 hours
  
  OR
  
  - **moxifloxacin**: 400 mg orally/intravenously once daily

International guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend antibiotics for people with acute exacerbations of COPD and an increase in sputum purulence, plus an increase in sputum volume, and/or increased dyspnea.[1]

Some patients with COPD may keep antibiotics at home for use in an exacerbation as part of their self-management plan.[140]

Patients with more severe exacerbations, particularly those requiring treatment in the intensive care unit (ICU), have been shown to derive greater benefit from antibiotic therapy.[181] International guidelines from GOLD recommend that antibiotics should be given to patients with severe exacerbations requiring mechanical ventilation (invasive or noninvasive).[1]

Patients with more severe underlying COPD, and those with greater exacerbation severity, are more often colonized with gram-negative bacteria such as *Pseudomonas aeruginosa* or other enteric gram-negative organisms and/or *Staphylococcus aureus* (including meticillin-resistant *Staphylococcus aureus*).[74] Therefore, broad-spectrum antibiotics such as ampicillin/sulbactam, piperacillin/tazobactam, vancomycin, and fluoroquinolones are considered for patients at greater risk for a poor outcome, or with an episode of greater severity.[74] [137] Agents with activity against *Pseudomonas aeruginosa* are also indicated for people at risk of this infection.[37] The choice of antibiotic should also be based in part on local bacterial resistance patterns.
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Sputum cultures or endotracheal aspirates (in patients who are intubated) are recommended for assessment of bacterial infection in patients with severe lung function impairment, those with a history of frequent exacerbations, and/or in patients hospitalized with COPD exacerbations or who require mechanical ventilation, as gram-negative bacteria (such as *Pseudomonas* species) or resistant pathogens may be present. Consideration may also be given to obtaining a sputum culture in patients who have bronchiectasis and suspected infectious exacerbations as a feature of their COPD.

Risk factors for a poor outcome include recent history of antibiotic use, more severe baseline COPD, need for hospitalization, treatment failure, prior antibiotic resistance, or risk factors for healthcare-associated infections. Critically ill patients in the ICU are also at higher risk.

Use of accessory muscles of respiration, paradoxical respirations, cyanosis, new peripheral edema, hemodynamic instability, and worsened mental status (e.g., confusion, lethargy, coma) are important indicators of a more severe exacerbation.

Patients who receive antibiotics are at increased risk for antibiotic-associated diarrhea, compared with placebo, although the difference is not statistically significant.

Antibiotic choice and duration of therapy is an unresolved issue, but in general should be based on local resistance patterns and patient characteristics, including any previous culture results for the patient. The most common bacterial pathogens include: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. When indicated, GOLD recommends that the duration of antibiotic therapy should be 5 to 7 days, but local guidelines should be consulted.

If the patient's dyspnea and/or sputum purulence improve, this suggests that the antibiotic is effective. Guidelines from the National Institute for Health and Care Excellence (NICE) recommend that, if intravenous antibiotics are given, they should be reviewed within 48 hours and stepped down to oral antibiotics where possible.

Antibiotic-resistant bacteria should be considered, and a sputum sample sent for microscopy, culture, and Gram stain if necessary.
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≤7.35); severe dyspnea with signs that suggest fatigue of respiratory muscles, or increased work of breathing, or both, such as the use of accessory muscles of respiration, paradoxical movement of the abdomen, or retraction of the intercostal spaces; persistent hypoxemia while on supplemental oxygen.[1]

» Improvements in the patient's level of dyspnea and physiologic state are typically seen within 1 to 4 hours.[203] The Global Initiative for Chronic Obstructive Lung Disease report recommends that if patients improve and can breathe unassisted for at least 4 hours, then NIV can be stopped.[1]

» However, NIV is not successful for all patients, and clinicians should discuss the risks and benefits of invasive mechanical ventilation with patients receiving NIV to determine their desired course of treatment.

adjunct invasive mechanical ventilation

Treatment recommended for SOME patients in selected patient group

» Severity depends on the patient's prior status and any changes to previous baseline investigation (based on symptoms, examination, lung function, ABG). Use of accessory muscles of respiration, paradoxical respirations, cyanosis, new peripheral edema, hemodynamic instability, and worsened mental status (e.g., confusion, lethargy, coma) are important indicators of a more severe exacerbation.[1] [54]

» Noninvasive mechanical ventilation (NIV) may fail. Invasive mechanical ventilation should be considered for patients with outright respiratory or cardiac arrest, who are in or have signs of impending acute respiratory failure despite NIV, have impaired mental status or cardiovascular instability, are at high risk for aspiration, or for whom NIV cannot be appropriately applied (e.g., craniofacial trauma, recent gastroesophageal surgery, copious secretions, anxiety disorder, facial discomfort, or severe skin breakdown). [204]

» Physiologic criteria for invasive mechanical ventilation include the following: life-threatening hypoxemia in patients unable to tolerate NIV, inability to tolerate NIV or failure of NIV, respiratory or cardiac arrest, irregular breathing with gasping or loss of consciousness, massive aspiration or persistent vomiting, inability to clear respiratory secretions, heart rate <50 beats per minute with diminished alertness,
Acute exacerbation of chronic obstructive pulmonary disease

Management

Acute severe hemodynamic instability not responsive to medical treatment, or severe ventricular or supraventricular arrhythmias.[1] [205]

» The risk for mortality is significant (11% to 49%) for people with severe disease in whom invasive mechanical ventilation is indicated.[12] [206] Complications of mechanical ventilation include ventilator-associated pneumonia and barotrauma.

» Weaning patients with severe COPD from mechanical ventilation can be difficult.[204] Use of NIV to assist weaning from mechanical ventilation can reduce weaning failure and nosocomial pneumonia, and may reduce mortality.[207] [208]
Acute exacerbation of chronic obstructive pulmonary disease

Management

Ongoing after stabilization

1st pulmonary rehabilitation and disease-management programs

- Patients with COPD who experience acute exacerbations of COPD often have skeletal muscle dysfunction, potentially due to limited physical activity, nutritional disturbances, corticosteroid use, and/or systemic inflammatory factors.[212] [213]

- Pulmonary rehabilitation is a multidisciplinary program of care that involves physical rehabilitation as well as guidance on disease management, nutrition, and other lifestyle issues (e.g., smoking cessation, medication adherence and inhaler technique, supplemental oxygen, and maintenance of physical activity).[214] [215]

- As COPD patients and their exacerbations are highly heterogeneous, determining who may benefit from respiratory rehabilitation varies greatly according to the comorbidities and other characteristics of each patient.

- Selected forms of exercise rehabilitation initiated during a hospitalization for COPD exacerbation, including resistance strength training and transcutaneous electrical muscle stimulation, are well tolerated and can prevent muscle function decline and hasten functional status recovery.[216] [217] [218]

- Pulmonary rehabilitation initiated early during the recovery phase of an exacerbation is safe and effective, and leads to improvements in exercise tolerance, physical abilities, the degree of symptoms due to COPD, and quality of life.[219] [220] [221] [222] [223] [224] [225] [226]

- Comprehensive supervised pulmonary rehabilitation in the outpatient setting in the post-exacerbation period also decreases the risk for future hospitalization.[215] [222] [223] [227] Participation in pulmonary rehabilitation within 90 days of discharge following hospitalization for COPD exacerbation is associated with a significant decrease in mortality risk.[228] Unsupervised, home-based exercise training following exacerbations does not appear to confer the same benefits.[229]

- Disease management programs can be helpful, but their use remains controversial given that a randomized controlled trial had to be stopped early due to a noted increase in mortality in the comprehensive care
management group, as compared with control patients who were receiving guideline-based routine medical care.[214] [230] [231] [232] [233] Another study involving unsupervised home-based exercise training following hospitalization for acute COPD exacerbation also showed a mortality signal at the 6-month post-hospitalization time point.[229]

» Some data is emerging that hospital-at-home care with support from respiratory nurses may be appropriate for selected people with moderate exacerbations of COPD.[234] However, this approach is not yet considered the standard of care, and people with unstable vital signs, decompensated gas exchange, acute respiratory acidosis, worsened hypoxemia, change in mental status, or significant comorbid illness are not suitable for this approach.[95] [235]

» A randomized controlled trial has suggested that the use of nurse-centered tele-assistance may decrease the occurrence of exacerbations of COPD and hospitalization. The use of such programs may be cost-saving.[236] However, another randomized controlled trial demonstrated that tele-monitoring integrated into existing clinical services did not reduce hospital admissions or improve patients’ quality of life.[237]

Primary prevention

Given the detrimental impact of COPD exacerbations on the patient, every effort should be made to prevent their occurrence. Previous exacerbation history is a key risk factor for future exacerbations.[1] [21] People with a high burden of symptoms and history of frequent exacerbations (Global Initiative for Chronic Obstructive Lung Disease [GOLD] group D) are at particular risk of future exacerbations and mortality.[1] [90] However, multiple factors impact the risk of subsequent exacerbations and relevant factors vary among individual patients. Following COPD exacerbation, every effort should be made to both identify and intervene in potentially modifiable factors to reduce risk of subsequent exacerbation events. In addition to identifying and avoiding potential triggers, adjustments to pharmacotherapy may be warranted.

Smoking cessation

• Avoiding smoke and smoking cessation are the best measures not only to prevent the onset of COPD, but also to prevent progression of the severity of COPD.[78] [79] More severe COPD is associated with both more frequent and more severe exacerbations.[21] [91] Smoking cessation can also reduce risk of exacerbations, and smoking cessation, counseling, and treatment is recommended for people with COPD.[80] [81]

Trigger avoidance

• Patients should also be advised to avoid other potential triggers, such as wood smoke, dust, and other airborne pollutants.
Acute exacerbation of chronic obstructive pulmonary disease

Management

Immunization

- There is evidence that influenza vaccination is effective in preventing complications of COPD, particularly among people with severe airflow obstruction.\[92\]\[93\]\[94\]\[95\] Yearly influenza vaccine is recommended for adults with COPD.\[81\] The benefits of pneumococcal vaccination in reducing overall morbidity from COPD (including exacerbations) is less clear, but the vaccine does reduce the risk of pneumococcal pneumonia.\[81\]\[96\]\[95\] One updated Cochrane review concluded that pneumococcal vaccination in people with COPD reduced the chance of an acute exacerbation and provided some protection against community-acquired pneumonia.\[97\] Pneumococcal vaccination with PPSV23 (23-valent pneumococcal polysaccharide vaccine) is recommended for all patients 65 years of age and older. The PPSV23 is also recommended for younger patients with COPD who have significant comorbidities, such as chronic heart or lung disease.\[1\]\[81\] In the US, shared decision-making is recommended regarding administration of the PCV13 (13-valent conjugated pneumococcal vaccine) to people aged 65 years and older who do not have an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant, and who have not previously received PCV13. If a decision to give PCV13 is made, PCV13 should be given first, followed by PPSV23 at least 1 year later.\[98\] The indications and benefits of vaccination against influenza virus, and \textit{Streptococcus pneumoniae}, should be discussed with the patient.\[92\]\[93\]\[99\]

- Some data suggest that an oral \textit{Haemophilus influenzae} vaccine may help reduce recurrent exacerbations of chronic bronchitis in selected patients.\[100\]\[101\]\[102\]\[103\]\[104\] However, one Cochrane review analysis demonstrated that oral \textit{H influenzae} vaccine did not significantly reduce the number or severity of exacerbations.\[105\]

Pharmacotherapy

- A primary goal of treating stable COPD is to reduce symptoms and future risk of exacerbations. A stepwise approach to inhaled pharmacotherapy is recommended, based on symptoms and exacerbations.\[1\]

- Please see the BMJ Best Practice topic COPD for further details on the management of stable COPD.

Supplemental oxygen and noninvasive ventilation

- Assessment of oxygenation during rest, exertion, and sleep is warranted for individuals with recurrent acute exacerbations of symptoms. Episodes of hypoxemia may increase ventilatory demand and trigger dyspnea, dynamic hyperinflation, and potentially, respiratory failure.\[106\] Arterial blood gas testing is helpful to identify people who have ventilatory insufficiency contributing to their symptoms, and who may benefit from, and/or require, noninvasive ventilation.\[1\]

Secondary prevention

Pharmacotherapy

- Once the patient has stabilized following treatment for an exacerbation, the patient’s maintenance medications should be reviewed, and consideration given to adjusting the medications following exacerbations. The goal should be to reduce the risk and/or severity of future episodes, as well as the use of medications according to evidence-based guidelines.\[81\]\[1\]

- One meta-analysis has shown that vitamin D supplementation reduced the rate of moderate/severe COPD exacerbations in patients with baseline 25-hydroxyvitamin D levels (<25 nmol/L [<10 ng/ml]) but not in those with higher levels.\[259\] International guidelines from the Global Initiative for Chronic Obstructive Lung Disease therefore recommend that vitamin D levels be measured for patients hospitalized for exacerbations of COPD, and supplements provided for those with severe deficiency (vitamin D levels <25 nmol/L [<10 ng/ml]).\[1\]

Pulmonary rehabilitation and disease-management programs

- Patients nonadherent with their medication regimens may develop worsening of signs and symptoms associated with COPD. It is important to discuss and determine adherence with medications in patients presenting with acute exacerbations.\[260\] Failure to adhere to prescribed medications may
be associated with increased healthcare costs.[261] Moreover, healthcare providers do not always adhere to existing guidelines for management of stable COPD or acute COPD exacerbations.[262] This, in turn, may impact COPD exacerbation outcomes. Insufficient peak inspiratory flow rate can lead to suboptimal efficacy of inhaled medications. Consideration should be given to measurement of peak inspiratory flow rate during outpatient clinic visits to see if flow rates are adequate to entrain the patients’ current maintenance bronchodilator, or whether substitution of alternate agents may be needed.[263]

- Also, patients with COPD are less physically active than healthy adults and low physical activity levels are associated with a faster rate of decline in lung function and increased hospitalizations for COPD exacerbations over time.[252] [264] [265] Pulmonary rehabilitation programs provide exercise reconditioning and education focused on health-enhancing behaviors that can improve patients’ physical activity levels and knowledge regarding management of their disease.[215] [266] As such, patients’ participation in pulmonary rehabilitation programs can play an important role in prevention of subsequent exacerbations, particularly when undertaken within a month following an exacerbation.[252] [260] [267] [81] [222] Participation in pulmonary rehabilitation within 90 days of discharge following hospitalization for COPD exacerbation is associated with a significant decrease in mortality risk.[228]

- Outpatient follow-up of patients within 30 days of hospital discharge following acute exacerbations also helps prevent readmissions and relapse of disease.[256] Action plans can help patients recognize worsening symptoms, initiate earlier treatment, and reduce overall impact of exacerbations.[81] [268] Enrollment of patients in disease-management and integrated care programs can also be effective in reducing emergency visits and/or hospitalizations for COPD exacerbations.[214] [230] [231] However, their use remains somewhat controversial given that some trials have not shown any increase in time to hospital readmission.[269] One randomized controlled trial had to be stopped early due to a noted increase in mortality in the patient group randomized to comprehensive care management compared with the control group receiving guideline-based routine clinical care.[95] [233] Self-management programs offered immediately after acute exacerbations are associated with positive effects on patients’ knowledge, but based on existing evidence it is not possible to draw firm conclusions regarding their efficacy for other outcomes.[270] Education with management that includes direct access to a healthcare specialist at least monthly is recommended by evidence-based guidelines for patients with previous or recent exacerbations to reduce subsequent severe exacerbations requiring hospitalization.[81] The benefits of disease management programs likely vary depending on program content and structure, the healthcare system in which they are implemented, and the patient population being studied. The role of hospital-at-home programs in the management of COPD exacerbations is being studied.[95] [235]

- Tele-health has been used for home-based disease monitoring and management intervention.[271] Randomized controlled trials have suggested that the use of nurse-centered tele-assistance may decrease the occurrence of exacerbations of COPD, urgent care visits, and hospitalization.[271] The use of such programs may be cost-saving.[236] Other analyses have suggested that home tele-monitoring may prolong the time free of hospitalizations or ER visits, but the total number of hospitalizations may not be affected and another randomized controlled trial showed no clear beneficial effects.[95] [237] A video tele-health pulmonary rehabilitation intervention, given early after hospitalization for COPD exacerbation, was associated with significantly lower 30-day, all-cause re-admission rates.[272] Heterogeneity of existing studies precludes development of any firm generalizable conclusions regarding the role of tele-health in the prevention or treatment of exacerbations, and as such it is not currently recommended for exacerbation prevention.[273] [1] [81]

### Patient discussions

Patients often under-report symptoms of acute exacerbation.[257] Patients should be asked regularly at clinic visits about escalation of symptoms, and educated about the difference between the expected day-to-day variation in symptoms, symptoms of “dyspnea crisis” (related to dynamic hyperinflation), and symptoms heralding a COPD exacerbation. “Dyspnea crisis” is defined as a sustained and severe resting breathing discomfort that occurs in patients with advanced, often life-limiting illness and overwhelms the patient and caregivers’ ability to achieve symptom relief.[258] Dyspnea crisis and dynamic hyperinflation can also occur among those with mild airflow obstruction (e.g., during exercise) as well as other causes of faster respiratory rate (e.g., during periods of anxiety).
Patients should be advised to contact their clinician if they experience fever, worsening of their respiratory status beyond usual day-to-day variation, and/or a significant increase in their production of purulent sputum. If patients are receiving systemic corticosteroids and are known to be diabetic, they should be advised to closely monitor their blood glucose and contact their clinician if it is outside the prescribed range. If patients are prescribed antibiotics, they should be advised to contact their clinician if they develop diarrhea, as antibiotic-associated colitis, which may be due to *Clostridium difficile*, is a recognized complication of exposure to antibiotics.
Monitoring

Patients experiencing an acute exacerbation of COPD should be followed closely to ensure continued improvement and resolution of the associated signs and symptoms. When possible, persons hospitalized with COPD exacerbation should be seen by a healthcare provider within 30 days of hospital discharge.[256] Clinicians should consider the potential need for adjustment of each patient’s medication regimen for COPD, as patients experiencing an acute exacerbation occasionally do not return rapidly to their baseline level of health. Efforts should be made to ensure patients are educated regarding adherence with their medication regimens and that they have received appropriate vaccinations (e.g., influenza, pneumococcus).

Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>mechanical ventilation and ventilator-associated pneumonia</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Patients who are ventilated are at high risk of infection. May be due to aspiration following intubation and/or related to bypassing normal anatomic structures involved in host defense.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antibiotic-related diarrhea</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Antibiotic-associated colitis, which may be due to Clostridium difficile, is a recognized complication of exposure to antibiotics.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mechanical ventilation and ventilator-associated barotrauma</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Occurs due to mechanical ventilation, and is the development of extra-alveolar air. Careful use of ventilator settings, including use of lower tidal volumes, faster inspiratory flow rates, and monitoring airway pressures may help prevent the occurrence of this complication.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypotension due to mechanical ventilation</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Occurs due to increased intrathoracic pressure and increased dynamic hyperinflation, leading to decreased venous return to the heart, often in conjunction with relative volume depletion and/or use of anxiolytic and/or narcotic medications.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cor pulmonale</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>This may develop as a result of increased hypoxic vasoconstriction due to exacerbation-induced hypoxemia. The resulting increase in pulmonary vascular resistance and/or pulmonary artery pressure can lead to acute right heart failure. Elevated jugular venous pressure, hepatojugular reflux, peripheral edema, and relative hypotension may be present.</td>
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Prognosis

There is a broad spectrum of severity of disease encompassed by people with COPD. Likewise, acute exacerbations range from very mild to severe and life-threatening. Morbidity and mortality among people with COPD occurs most often in the context of exacerbations. Older studies have estimated mortality rates of 4% to 30% among patients hospitalized for acute exacerbations. A study based on data available from the 1996 Nationwide Inpatient Sample (Agency for Healthcare Research and Quality, Rockville, MD) found in-hospital mortality for people with an acute exacerbation to be 2.5% overall.[247] In this study, the median duration of hospitalization was 5 days and 70% of patients were discharged to home without additional in-home health services. Patients who died during hospitalization were shown to be older, had greater levels of underlying comorbidities, and were hospitalized for longer periods. Not surprisingly, a greater rate of mortality was shown for patients who were mechanically ventilated compared with those who were not (28% versus 1.7%). Another study identified an approximately 50% 5-year mortality following hospitalization for COPD exacerbation.[248] Rehospitalization and/or mortality have been associated with lower FEV1, higher partial pressure of carbon dioxide, lower partial pressure of oxygen, greater APACHE II score, lower BMI, older age, comorbidities, and low physical activity levels.[206] [249] [250] [251] [252] [253] [254] The multidimensional CODEX (comorbidity, obstruction, dyspnea, previous severe exacerbations) index can predict readmission and survival at 3 months and 1 year after hospitalization for COPD exacerbation.[255]
Diagnostic guidelines

International

Veterans Affairs/Department of Defense clinical practice guideline: the management of chronic obstructive pulmonary disease (http://www.healthquality.va.gov/) [137]

Published by: US Department of Veterans Affairs and US Department of Defense Last published: 2014

Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (http://goldcopd.org/2021-gold-reports/) [1]

Published by: Global Initiative for Chronic Obstructive Lung Disease Last published: 2021

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (https://www.nice.org.uk/guidance/ng115) [138]

Published by: National Institute for Health and Care Excellence (UK) Last published: 2019
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**Guidelines**

## Treatment guidelines

### International

- **ACR appropriateness criteria: acute respiratory illness in immunocompetent patients** ([http://www.acr.org/Quality-Safety/Appropriateness-Criteria](http://www.acr.org/Quality-Safety/Appropriateness-Criteria))  [239]
  - **Published by:** American College of Radiology
  - **Last published:** 2018

- **Screening for chronic obstructive pulmonary disease: U.S. Preventive Services Task Force recommendation statement** ([https://jamanetwork.com/journals/jama/issue/315/13](https://jamanetwork.com/journals/jama/issue/315/13))  [240]
  - **Published by:** US Preventive Services Task Force, Agency for Healthcare Research and Quality
  - **Last published:** 2016

  - **Published by:** US Department of Veterans Affairs; US Department of Defense
  - **Last published:** 2014

  - **Published by:** Canadian Thoracic Society
  - **Last published:** 2010

  - **Published by:** Canadian Thoracic Society
  - **Last published:** 2008

  - **Published by:** American College of Chest Physicians; American Association of Cardiovascular and Pulmonary Rehabilitation
  - **Last published:** 2007

- **Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines** ([https://journal.chestnet.org/issue/S0012-3692(15)X6430-0](https://journal.chestnet.org/issue/S0012-3692(15)X6430-0))  [243]
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  - **Last published:** 2006

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### International

**Chronic cough due to chronic bronchitis: ACCP evidence-based clinical practice guidelines** (https://journal.chestnet.org/issue/S0012-3692(15)X6430-0) [245]

**Published by:** American College of Chest Physicians  \n**Last published:** 2006

**Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease** (http://goldcopd.org/2021-gold-reports/) [1]

**Published by:** Global Initiative for Chronic Obstructive Lung Disease  \n**Last published:** 2021

**Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline** (https://www.ersnet.org/guidelines/)

**Published by:** European Respiratory Society; American Thoracic Society  \n**Last published:** 2017

**Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline** (https://www.ersnet.org/guidelines/)

**Published by:** European Respiratory Society; American Thoracic Society  \n**Last published:** 2017


**Published by:** American Thoracic Society/European Respiratory Society  \n**Last published:** 2015


**Published by:** American Thoracic Society; European Respiratory Society  \n**Last published:** 2013

**An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation** (https://www.ersnet.org/guidelines/)

**Published by:** European Respiratory Society; American Thoracic Society  \n**Last published:** 2013

**Chronic obstructive pulmonary disease in over 16s: diagnosis and management** (https://www.nice.org.uk/guidance/ng115) [138]

**Published by:** National Institute for Health and Care Excellence (UK)  \n**Last published:** 2019

**Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing** (https://www.nice.org.uk/guidance/ng114) [140]

**Published by:** National Institute for Health and Care Excellence (UK)  \n**Last published:** 2018
International

Guidelines for the management of adult lower respiratory tract infections
(http://www.sciencedirect.com/science/article/pii/S1198743X1461404X)  [37]

Published by: European Respiratory Society; European Society for Clinical Microbiology and Infectious Diseases

Last published: 2011
**Key articles**


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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style
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