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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.

May represent the first presentation of COPD, usually associated with a history of tobacco exposure.

Treatment includes bronchodilators, systemic corticosteroids, and antibiotics.

Antibiotics may be reserved for exacerbations thought to be due to bacteria. An acute change in the volume and color of sputum produced is suggestive of a bacterial trigger.

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).
Acute exacerbation of chronic obstructive pulmonary disease

Basics

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."[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 bacterial or viral pathogens, pollutants, 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] Exacerbation rates and all-cause mortality tend to be higher during winter months.[18] 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.[19] [20] [21] [22] [23] Early deaths among patients hospitalized with severe COPD exacerbation are often caused by concurrent problems such as pulmonary embolus, pneumonia, or CHF.[24] Patients may also be at risk of myocardial infarction and stroke in the post-exacerbation period.[25]

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] [26] 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 gender, genetic and socioeconomic factors, as well as exposures to dusts, chemicals, and pollutants, and early childhood severe respiratory infection. Acute exacerbations of COPD occur intermittently throughout
Acute exacerbation of chronic obstructive pulmonary disease

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.[27] 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 cases.[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] [27] [28] However, exacerbations are diagnosed by the identification of typical signs and symptoms rather than by spirometry.[29]

Bacterial pathogens are thought to be responsible for triggering 50% to 70% of exacerbations. The most common bacterial pathogens include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis.*[27] [30] 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.[31] [32] [33] [34] The severity of baseline lung function impairment influences the profile of pathogens most likely to be present.[30]

Exacerbations may also be due to environmental pollutants such as smoke particulate matter, sulfur dioxide, nitrogen dioxide, and ozone.[35] [36]

**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,[37] 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.[38] [39] [40] The presence of microbial flora leads to antigen presentation and stimulation of the innate and then the adaptive immune response.[41] 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.[42] 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.[43] Hyperinflation that results from airflow limitation is a main cause of dyspnea.[44] Unlike asthma, airflow limitation in COPD is not fully reversible with medical therapy.[45] 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.[46] 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.[47] [48]

Acute exacerbations of COPD may be defined as an acute worsening of respiratory symptoms (e.g., dyspnea, cough, sputum production) that results in 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.[28] [49] [50] [51] 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.[1] [11] [52] Moreover, recovery from exacerbations may be prolonged, and some patients never regain their prior level of lung function and/or functional status.[10] There is evidence to suggest that exacerbations not only tend to be more frequent and more severe as COPD progresses,[53] [54] but may themselves accelerate the decline in lung function in COPD.[55] Indeed, some patients may also be at increased risk for COPD exacerbations (i.e., have a phenotype of increased susceptibility) independent of disease severity.[54] Currently recommended assessment of COPD patients includes 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.[1] Several additional factors are also associated with exacerbations and/or hospitalizations for COPD.[56] [57] COPD exacerbations, particularly those requiring hospitalization, are associated with increased mortality, as well as significant healthcare costs.[1]

**Classification**

**Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[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.

- **Group A**: low risk (0-1 exacerbation per year, not requiring hospitalisation) and fewer symptoms (mMRC 0-1 or CAT <10)
- **Group B**: low risk (0-1 exacerbation per year, not requiring hospitalisation) and more symptoms (mMRC ≥ 2 or CAT ≥ 10)
- **Group C**: high risk (≥2 exacerbations per year, or one or more requiring hospitalisation) and fewer symptoms (mMRC 0-1 or CAT <10)
- **Group D**: high risk (≥2 exacerbations per year, or one or more requiring hospitalisation) and more symptoms (mMRC ≥ 2 or CAT ≥ 10).
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.\[1\] [54] 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.\[1\] [78] 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.

Trigger avoidance, smoking cessation, and immunization

- 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.\[79\] [80] Smoking cessation can also reduce risk of exacerbations.\[81\] and smoking cessation counseling and treatment is recommended for people with COPD.\[82\] Patients should also be advised to avoid other potential triggers such as airborne pollutants. More severe COPD is associated with both more frequent and more severe exacerbations.\[54\] [83] There is evidence that influenza vaccination is effective in preventing complications of COPD,\[84\] [85] [86] particularly among people with severe airflow obstruction.\[87\] Yearly influenza vaccine is recommended for adults with COPD.\[82\] The benefits of pneumococcal vaccination in reducing overall morbidity from COPD (including exacerbations) is less clear,\[82\] [88] but the vaccine does reduce the risk of pneumococcal pneumonia.\[87\] An 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.\[89\] Pneumococcal vaccinations, PCV13 (13-valent conjugated pneumococcal vaccine) and PPSV23 (23-valent pneumococcal polysaccharide vaccine), are recommended for all patients over 65 years of age. The PPSV23 is also recommended for younger patients with COPD who have comorbidities such as chronic heart or lung disease.\[1\] [82] The indications and benefits of vaccination against influenza virus, and *Streptococcus pneumoniae*, should be discussed with the patient.\[84\] [85] [90]

Pharmacotherapy

- Once the patient has stabilized following treatment for an exacerbation, the patient’s maintenance medications should be reviewed and consideration should be given to adjusting the medications following exacerbations, with the goal of reducing the risk and/or severity of future episodes.\[82\] and use of medications according to evidence-based guidelines.\[1\] The use of long-acting beta-2 agonists and long-acting anticholinergic medications has been associated with a decreased frequency of exacerbations.\[91\] [92] [93] [94] [95] [96] [97] [98] [99] [100] [101] [102] [103] [104] [105] [106] [107] The long-acting anticholinergic agent tiotropium bromide may be more effective than the long-acting beta-2-agonist salmeterol in preventing exacerbations,\[108\] particularly among people with moderate-severity airflow obstruction.\[109\] The novel Respimat mist delivery system for tiotropium must, however, be used with caution, given that its use has been associated with a higher mortality rate.\[110\] The once-daily long-acting inhaled beta-2 agonist indacaterol is also effective in improving health status and reducing symptoms and exacerbations in COPD.\[111\] [112] [113] Another once-daily beta-2-agonist, olodaterol, has been approved for use in some countries, including the US.\[114\] Acclidinium bromide, a novel long-acting muscarinic antagonist, is also an effective bronchodilator that improves lung function, reduces symptoms, and reduces severe exacerbations requiring hospitalization.\[115\] [116] [117] Neither class of agent poses substantial increased risk of adverse cardiovascular events.\[105\] Combination dual-class bronchodilator therapy confers greater benefits on lung function than either individual class (long-acting beta-2-agonist or long-acting anticholinergic) alone.\[118\] However, it remains unclear whether a combination of dual-class bronchodilator therapy is more effective than long-acting antimuscarinic agents alone for reducing exacerbations.\[119\]

Novel combinations of a long-acting beta-2 agonist with a long-acting muscarinic antagonist (i.e., vilanterol/umeclidinium)\[120\] [121] are currently under investigation, but their efficacy in reducing the frequency and/or severity of exacerbations is as yet unknown.\[122\] Inhaled corticosteroids have been shown to decrease the frequency of exacerbations and decrease healthcare utilization for respiratory illnesses.\[123\] [124] [125] [126] [127] Inhaled corticosteroids should not be used as monotherapy in COPD; their use should be considered as additional therapy for people with exacerbations not controlled with long-acting bronchodilators alone.\[1\]
• The combination of inhaled corticosteroids and long-acting beta-2 agonists appears more effective than either agent alone to decrease the frequency of episodes in people with more severe COPD.[92][128][129] In patients with moderate to severe COPD, treatment with salmeterol plus fluticasone propionate reduces the rate of exacerbations and slows the progressive worsening of FEV1.[130][131][132] Importantly, withdrawal of the inhaled corticosteroid component of combination therapy led to deterioration in lung function and worsened symptoms among patients who had two or more exacerbations in the previous year.[133] A subsequent large parallel group study among patients with severe COPD and history of previous exacerbation showed similar risk of moderate or severe exacerbation among people who withdrew the inhaled corticosteroid from triple combination treatment gradually over a 12-week period, compared with controls who did not; inhaled corticosteroid withdrawal was, however, associated with a greater reduction in trough FEV1 at 18 weeks of follow-up.[134] Also, an increased risk of pneumonia has been reported following long-term use of inhaled corticosteroids and inhaled corticosteroid/beta-2 agonist combination therapy.[92][135][136][137][138][139] This increased risk of pneumonia is not accompanied by a clear increase in mortality risk.[139] Currently, there are limited but encouraging data on the concurrent use of inhaled corticosteroids, long-acting beta-2 agonists, and long-acting anticholinergic medications.[97][125][140][141][142][143][144][145][146] While long-acting beta-2 agonists, anticholinergics, and inhaled corticosteroids are all helpful, the optimal choice of medications to reduce exacerbations while minimizing potential adverse events remains somewhat uncertain,[135][147][148] and the impact of triple-class therapy as compared with dual-agent combination therapy or anticholinergic therapy alone on long-term outcomes such as mortality or hospitalizations is as yet unclear.[146][149] Novel combination therapies including fluticasone/vilanterol and indacaterol/glycopyrronium bromide are emerging, and their impact on exacerbations of COPD is currently being studied.

• Treatment of patients with intermittent doses of macrolide,[150][151] the fluoroquinolone moxifloxacin,[152][153] phosphodiesterase inhibitors[154][155] such as roflumilast, or statins[156][157][158] can also decrease the frequency, severity, and/or duration of COPD exacerbations. The short-term use of prophylactic antibiotics can reduce the rate and number of exacerbations of COPD or chronic bronchitis,[159] and preventative treatment with macrolides can lead to healthcare cost savings.[151] Daily azithromycin therapy was most effective in reducing exacerbations requiring both antibiotic and steroid treatment, and risk reduction was greatest among people of older age and milder GOLD grade, notably, no significant reduction of exacerbation risk was found among current smokers.[160] The impact of long-term use of intermittent (e.g., three-times weekly) macrolides or other prophylactic antibiotics on the development of antibiotic-resistant pathogens and related COPD exacerbations is as yet unknown but is of potential concern. Phosphodiesterase-4 (PDE4) inhibitor therapy is commonly associated with gastrointestinal upset, abdominal pain, weight loss, and other side effects; individual patient tolerance of these agents varies. Importantly, existing studies suggest that the PDE4 inhibitor roflumilast reduced exacerbations among patients with severe airflow obstruction with clinical features of chronic bronchitis (including sputum production and cough), but not among those with a predominance of emphysema without chronic bronchitis features.[161][162]

• Oral mucolytics such as N-acetylcysteine may offer benefit in exacerbation reduction, particularly among people with moderate to severe COPD and or history of two or more exacerbations in the previous 2 years, but their role remains controversial.[82][163][164] Alpha-1-antitrypsin augmentation therapy may reduce the frequency of exacerbations for selected people with documented alpha-1-antitrypsin deficiency as the etiology of their COPD.[165]

• Beta-blockers are often withheld from patients with COPD due to concerns regarding precipitation of exacerbations and bronchospasm. However, cardiovascular disease is a common comorbidity of COPD, and many patients have cardiovascular indications for beta-blocker therapy. Current data suggest that cardioselective beta-blockers are not only safe and effective in patients with COPD, but may reduce exacerbation risk and mortality.[166][167] Therefore, beta-blockers should not be withheld from patients with COPD who have cardiovascular indications for their use.

• Some data suggest that an oral *Haemophilus influenzae* vaccine may help reduce recurrent exacerbations of chronic bronchitis in selected patients.[168] However, one Cochrane review analysis demonstrated that oral *H influenzae* vaccine did not significantly reduce the number or severity of exacerbations.[169]

• Oral *Haemophilus* vaccines are not formally recommended in existing guidelines.[30] Prophylactic antibiotics to prevent exacerbations are also not recommended.

• Although retrospective studies suggested that statins might decrease the rate and severity of exacerbations, one large prospective randomized controlled trial of simvastatin versus placebo did not show a reduction in exacerbation rates or time to first exacerbation among people with history of...
Secondary prevention

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.[303] Failure to adhere to prescribed medications may be associated with increased healthcare costs.[304] Moreover, healthcare providers do not always adhere to existing guidelines for management of stable COPD or acute COPD exacerbations.[305] This, in turn, may impact COPD exacerbation outcomes.
- 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.[296] [306] [307] 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.[233] [308] As such, patients’ participation in pulmonary rehabilitation programs can play an important role in prevention of subsequent exacerbations,[296] [303] [309] particularly when undertaken within a month following an exacerbation.[82] [241]
- Outpatient follow-up of patients within 30 days of hospital discharge following acute exacerbations also helps prevent readmissions and relapse of disease.[300] Action plans can help patients recognize worsening symptoms, initiate earlier treatment, and reduce overall impact of exacerbations.[30] [310] Enrollment of patients in disease-management and integrated care programs can also be effective in reducing emergency visits and/or hospitalizations for COPD exacerbations.[232] [274] [275] However, their use remains somewhat controversial given that some trials have not shown any increase in time to hospital readmission,[311] and 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.[87] [277] 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.[312] Education with case 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.[82] 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.[87] [279]
- Tele-health has been used for home-based disease monitoring and management intervention.[313] 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.[313] The use of such programs may be cost-saving.[280] Other analyses have suggested that home tele-monitoring may prolong the time free of hospitalizations or ER visits,[87] but the total number of hospitalizations may not be affected and another randomized controlled trial showed no clear beneficial effects.[281] Heterogeneity of existing studies precludes development of any firm generalizable conclusions regarding the role of tele-health in the prevention or treatment of exacerbations,[314] and as such it is not currently recommended for exacerbation prevention.[1] [82]
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-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.

Step-by-step diagnostic 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;[10] or worsening of degree of cough, level of dyspnea, and/or the volume and character of sputum,[62] 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.[1] [171] [172] [173]

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 SaO2 via pulse oximetry), mental status, severity of the level of dyspnea and airflow obstruction, history of symptoms associated with the patient's chief complaints, and the ability to continue to provide self-care at home. 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); as well as 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
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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, and/or cyanosis) and/or signs of cor pulmonale, hemodynamic instability, or worsened mental status.

Laboratory evaluation and imaging

Diagnostic tests are typically reserved for those with moderate to severe exacerbations. Features of this include but are not limited to unstable vital signs, severe symptoms, low SaO₂ 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
- Chest radiograph
- ECG
- ABG
- CBC with platelets
- Electrolytes
- Creatinine
- BUN levels
- Sputum analysis.

In severe disease, a sputum Gram stain and culture should be obtained, and, if hospitalization is being considered and where feasible, tests for respiratory viruses should be conducted, to prevent healthcare-associated transmission of the pathogen (e.g., influenza, respiratory syncytial virus, and parainfluenza virus).

Emerging investigation

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.[174] Further research is required to establish its use in clinical practice.

Risk factors

Strong bacterial infection

- Bacterial pathogens are thought to be responsible for the majority of acute exacerbations of COPD. Evidence suggests that the presence of purulent sputum is frequently associated with a bacterial lower respiratory tract infection.[23] Because the lower respiratory tract in people with COPD is not sterile, the interpretation of culture results of both upper and lower respiratory tract specimens must be made
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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. [58] [59]

• The most frequently identified bacterial pathogens include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*. [30] [50] 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. [30] [60]

• Of note, it has been shown that acquisition of a new strain of bacteria by people with COPD is a risk for an acute exacerbation. [61] Alterations in the innate and/or adaptive immune response may result in cyclical perpetuation of inflammation and infection. [41]

• Concurrent infection with both bacterial and viral respiratory tract pathogens has been associated with more severe episodes. [49] Treatment of moderate to severe exacerbations with antibiotics has been associated with improved outcomes. [62] [63] Influenza vaccination may have protective effect in reducing risk of *Pseudomonas aeruginosa* infection. [30]

**gastroesophageal reflux/swallowing dysfunction**

• Gastroesophageal reflux and swallowing dysfunction with associated aspiration are common triggers for exacerbations of COPD. [64] [65] No available studies guide whether the treatment of reflux improves exacerbations of COPD.

**viral infection**

• It has been estimated that respiratory viruses are responsible for 22% to 50% of acute exacerbations. [32]

• 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. [30] [33] [34] [67]

• 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.

• 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. [69]

**pollutants**

• Increasing levels of 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. [73] [74] [75] Peaks of air pollution can also increase hospitalizations and mortality. [76]

• Exposure to many of these pollutants has been found to induce an inflammatory response in the respiratory tract. [27]

**Weak**
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atypical bacterial infection

• Atypical organisms (Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella species) have been associated with acute exacerbations though with conflicting results. 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. 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.

History & examination factors

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.

cough (common)

• A change in the character and frequency of cough is often identified. This change should be beyond day-to-day variations of the patient's typical cough.

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 exam. 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.

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 hx 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 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 smoke and whether they are currently smoking.

**past medical hx of gastroesophageal reflux/swallowing dysfunction (common)**
- It is important to determine if patients have a history of heartburn, bitter taste in the mouth, coughing or choking after eating, hiatal hernia, and/or gastroesophageal reflux or difficulty swallowing.[64] [65] However, gastroesophageal reflux 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.
- 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.[172] [175]
- 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 patients has a history of significant exposure to black smoke such as wood smoke, dust, and/or other pollutants.

**change in mental status (uncommon)**
- Including drowsiness, confusion, and/or personality change.

**fever (uncommon)**
- Signs of a bacterial infection (based on increased sputum purulence and/or volume) may be considered an indication for antimicrobial therapy.[1] In general, <50% of people with acute exacerbations experience fever.[23] [30] [34]
- The presence of a high and/or persistent fever should lead to consideration of the presence of bacterial pneumonia or influenza virus infection.
**Acute exacerbation of chronic obstructive pulmonary disease**

**Diagnosis**

**accessory muscle use (uncommon)**
- Sign of impending respiratory failure.

**paradoxical movements of abdomen (uncommon)**
- Sign of impending respiratory failure.
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SaO2 on pulse oximetry</strong></td>
<td>depressed below the patient's baseline level</td>
</tr>
<tr>
<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, SaO2 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>
<td></td>
</tr>
<tr>
<td><strong>chest radiograph</strong></td>
<td>hyperinflation, flattened diaphragms, increased retrosternal airspace, bullae, and a small, vertical heart</td>
</tr>
<tr>
<td>• Rarely diagnostic; principal purpose is to exclude alternate diagnoses. A CXR 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>
<td></td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>may be right heart enlargement, arrhythmia, ischemia</td>
</tr>
<tr>
<td>• Cardiovascular disease is common in people with COPD.[178] Additionally, the possibility of a myocardial infarction or pneumothorax 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>
<td></td>
</tr>
<tr>
<td><strong>Arterial blood gas</strong></td>
<td>respiratory acidosis and compensatory metabolic alkalosis</td>
</tr>
<tr>
<td>• Arterial blood gas (ABG) testing should be performed for people with a moderate to severe acute exacerbation of COPD, to detect chronic hypercapnia 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.[179]</td>
<td></td>
</tr>
<tr>
<td>• PaO2 &lt;60 mmHg indicates potential respiratory failure. PaO2 &lt;50 mmHg, PaCO2 ≥45 mmHg, or pH &lt;7.35 indicate a potentially life-threatening illness that requires consideration for intensive care and initiation of assisted ventilation.[180]</td>
<td></td>
</tr>
<tr>
<td><strong>CBC with platelets</strong></td>
<td>may show elevated hematocrit, elevated WBC count or anemia</td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td><strong>electrolytes, BUN, + creatinine</strong></td>
<td>usually normal</td>
</tr>
<tr>
<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.</td>
<td></td>
</tr>
</tbody>
</table>
## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>sputum culture + Gram stain</td>
<td>may suggest bacterial infection</td>
</tr>
<tr>
<td>• In severe disease, and if 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>respiratory virus diagnostics</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 in case of hospitalization, to identify the need for use of expanded infection control precautions.</td>
<td></td>
</tr>
<tr>
<td>cardiac troponin</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. [181]</td>
<td></td>
</tr>
<tr>
<td>CT scan of chest</td>
<td>normal if no pneumonia, pleural effusion, malignancy, or pulmonary embolus present</td>
</tr>
<tr>
<td>• May be useful to exclude alternate diagnoses, especially pulmonary embolus, if the diagnosis and basis of respiratory decompensation remains uncertain after routine CXR.</td>
<td></td>
</tr>
</tbody>
</table>

## Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>procalcitonin</td>
<td>may be elevated</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. [174] Further research is required to establish its use in clinical practice.</td>
<td></td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Congestive heart failure| • Patients with systolic left-sided or biventricular congestive heart failure will often have a history of 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.[182] It may be difficult to distinguish heart failure, particularly left-sided heart failure, from an acute exacerbation of COPD. | • Chest imaging may show an enlarged heart, pulmonary vascular congestion, and/or pleural effusions. An elevated B-type natriuretic peptide is often present.[183]  
  [184] An echocardiogram may be used to determine cardiac function.                                                                                                           |
| Pneumonia               | • Many aspects of acute exacerbations 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.[185]  
  [186] [187] 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 pneumonia.[185] [188] The presence of pneumonia as a cause of respiratory decompensation in a patient with COPD does not necessarily imply the presence of a COPD. | • Chest imaging in patients with pneumonia should identify changes consistent with an infiltrative process in the lung parenchyma.                                                                                         |
## Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute 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>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>• Pleural effusions may exacerbate dyspnea in patients with COPD. Physical exam 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. [189]</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. [190] 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 thromboembolic disease or underlying malignancy may be at particular risk. [190] • A low systolic blood pressure and/or the inability to increase the PaO2 to &gt;60 mmHg with oxygen may</td>
<td>• 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>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>------------------------</td>
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<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acute exacerbation of chronic obstructive pulmonary disease</td>
<td>indicate the presence of a pulmonary embolism.</td>
<td></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 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;</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.</td>
</tr>
<tr>
<td>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>----------------------------------------</td>
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</tr>
<tr>
<td></td>
<td>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></td>
</tr>
<tr>
<td>Inappropriate oxygen therapy</td>
<td>• While oxygen therapy is clearly indicated for many patients with COPD and acute exacerbations, 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 and/or intrapulmonary shunt. An excess of oxygen may also decrease the capacity of erythrocytes to carry CO2 (Haldane effect). These changes may then result in worsening of the patient’s hypercarbia and respiratory acidosis. Selected patients with impaired respiratory drive may also develop worsening hypercarbia.</td>
<td>• An ABG should be performed for patients who are hypoxemic or are receiving oxygen therapy who present with an apparent acute exacerbation of COPD.</td>
</tr>
</tbody>
</table>

**Diagnostic criteria**

**Assessment of severe exacerbations**

Severity depends on patient's prior status and any changes to previous baseline investigation (based on symptoms, examination, lung function, ABG). Use of accessory respiratory muscles, paradoxical respirations, cyanosis, new peripheral edema, hemodynamic instability, and/or worsened mental status (e.g., confusion, lethargy, coma) are important indicators of severity of exacerbation.[1]
Step-by-step treatment approach

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. Short-acting beta-2 agonists and anticholinergic medications are considered first-line therapy, and may provide benefit within 15 and 30 minutes, respectively. If the patient remains symptomatic, repeat doses may be given. There are as yet no clinical trials to guide whether long-acting bronchodilators should be continued during acute COPD exacerbation. 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. Supplemental oxygen may be needed if the patient is hypoxic, although oxygen should be applied with caution to prevent further hypercarbia. Careful titration of supplemental oxygen even in the pre-hospital setting (e.g., en route to the hospital) is important to prevent worsening respiratory acidosis, which may increase mortality.[197]

Systemic corticosteroids decrease airway inflammation and have been shown to be beneficial for patients with acute exacerbation of COPD.[125] [198] [199] [200] [201] They enhance early (within 3 days) improvements in symptoms and lung function, reduce treatment failures and early (within 1 month) relapses, and reduce hospital length of stay.[199] Systemic corticosteroids should be initiated after the first treatment of short-acting inhaled bronchodilators. However, studies examining the role of systemic corticosteroids have been primarily performed among people presenting to emergency rooms and those who are hospitalized. The shortest duration of systemic corticosteroids that confers clinical benefit while minimizing adverse effects remains unclear.[202] The balance of risks and benefits of corticosteroids for people with milder exacerbations is uncertain. Moreover, 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.[203]

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.

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.[1] [204]

While methylxanthine medications may provide benefit to some people with COPD,[205] [206] 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.[207]

The use of mucolytics, expectorants, and/or physical mucus-clearing techniques does not appear to provide any clear proven benefit,[208] [209] although some patients do experience symptomatic relief.

COPD patients and their exacerbations are highly heterogeneous. While many aspects of their 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 vary greatly according to the comorbidities and other characteristics of the individual patient.
Acute exacerbation of chronic obstructive pulmonary disease

Hospitalization should be considered for people with marked or sudden increase in symptom severity, severe underlying COPD, or new physical signs (such as peripheral edema or cyanosis); those who have a history of frequent exacerbations or comorbid illness; those who are of older age; or those who fail to respond to initial outpatient management or have suboptimal home support.[1]

**Exacerbations with suspected bacterial etiology**

Bacterial infections are thought to be a common trigger.[61] Multiple randomized placebo-controlled trials have shown that antibiotics are beneficial for the treatment of patients with acute exacerbation of COPD.[62] [210] [211] Antibiotics should be given to patients suspected of having a bacterial trigger.[12] A bacterial trigger may be present in people with two or more of the following: increased sputum purulence, increased sputum volume, or worsening dyspnea.[45] [176] [194] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend antibiotics for people with a combination of increased dyspnea, increased sputum volume, and increased sputum purulence, or for those with increased sputum purulence combined with one of the other two criteria noted above.[1] 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.[62] [212] antibiotics should be given to patients with severe exacerbations requiring mechanical ventilation (invasive or noninvasive).[1] However, patients who receive antibiotics are at increased risk for antibiotic-associated diarrhea.[212] Antibiotic choice and duration of therapy is an unresolved issue, but in general should be based on local resistance patterns and patient characteristics.[194] The NHLBI/WHO (National Heart, Lung and Blood Institute/World Health Organization) workshop recommended choosing specific antibiotics based on local susceptibility patterns of common bacteria associated with exacerbations: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.[45] It has been recommended that more narrow-spectrum antibiotics (e.g., amoxicillin, amoxicillin/clavulanate, doxycycline, tetracycline, second-generation cephalosporins, macrolides, trimethoprim/sulfamethoxazole) be considered for patients at less risk for a poor outcome and with an exacerbation of lesser severity. 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*).[60] Therefore, extended-spectrum beta-lactam combination drugs, fluoroquinolones, and vancomycin are considered for patients at greater risk for a poor outcome or with an episode of greater severity, such as people with recent history of antibiotic use, treatment failure, prior antibiotic resistance, or risk factors for healthcare-associated infections, or critically ill patients in the ICU.[194] 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.[213] [214] [215] [216] [217] [218] There is currently insufficient evidence to guide use of antibiotics based on serum procalcitonin levels in patients with COPD.[194]

**Severe exacerbations of COPD**

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

In addition to the general measures, patients with severe exacerbations who do not appear to respond sufficiently to the initial interventions should be considered for noninvasive positive-pressure ventilation (NPPV). The use of NPPV for patients with acute exacerbations of COPD and respiratory failure has been
Acute exacerbation of chronic obstructive pulmonary disease

**Treatment**

NPPV use should be considered for patients with one or more of the following:[1]

- Respiratory acidosis (PaCO₂ ≥ 6.0 kPa or 45 mmHg and arterial pH ≤ 7.35)
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work or breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces
- Persistent hypoxemia despite supplemental oxygen therapy.

In some patients, NPPV may fail. Invasive mechanical ventilation via endotracheal intubation should be considered for patients who have outright respiratory or cardiac arrest, are in or have signs of impending acute respiratory failure despite NPPV, have impaired mental status or cardiovascular instability, are at high risk for aspiration, or for whom NPPV cannot be appropriately applied (e.g., craniofacial trauma, recent gastroesophageal surgery, copious secretions, anxiety disorder, facial discomfort, or severe skin breakdown).[225] Physiologic criteria for invasive mechanical ventilation include the following: severe hypoxia, inability to tolerate NPPV or failure of NPPV, 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] [226] The risk for mortality is significant (11% to 49%) for people with severe disease in whom invasive mechanical ventilation is indicated.[12] [227] Complications of mechanical ventilation include ventilator-associated pneumonia and barotrauma. Weaning patients with severe COPD from mechanical ventilation can be difficult.[225] Use of NPPV to assist weaning from mechanical ventilation can reduce weaning failure and nosocomial pneumonia, and may reduce mortality.[224] [228]

**Pulmonary rehabilitation**

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 compliance and inhaler technique, supplemental oxygen, and maintenance of physical activity).[232] [233] [234]

- 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.[235] [236] [237]
- 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.[238] [239] [240] [241] [242]
- Comprehensive supervised pulmonary rehabilitation in the outpatient setting in the post-exacerbation period decreases the risk for future hospitalization and may reduce mortality.[233] [241] [242] [243] Unsupervised home-based exercise training following exacerbations does not appear to confer the same benefits.[244]

**Treatment details 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

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### Acute

#### at presentation

1st short-acting bronchodilator  
plus systemic corticosteroid  
adjunct airway clearance techniques  
adjunct oxygen

- suspected bacterial etiology (exacerbation of lesser severity)  
  adjunct narrow-spectrum antibiotic

- suspected bacterial etiology (exacerbation of greater severity)  
  adjunct broad-spectrum antibiotic

- respiratory insufficiency  
  adjunct noninvasive positive-pressure ventilation  
  adjunct invasive positive-pressure ventilation

### Ongoing

#### after stabilization

1st pulmonary rehabilitation and disease-management programs
Treatment options

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.
### Treatment

**Acute at presentation**

<table>
<thead>
<tr>
<th>1st short-acting bronchodilator</th>
<th>Primary options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» <strong>albuterol inhaled</strong></td>
<td>2.5 to 5 mg nebulized every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing; (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing</td>
</tr>
<tr>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» <strong>levalbuterol inhaled</strong></td>
<td>0.63 to 1.25 mg nebulized every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing; (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing</td>
</tr>
<tr>
<td>--AND/OR--</td>
<td></td>
</tr>
<tr>
<td>» <strong>ipratropium bromide inhaled</strong></td>
<td>0.25 to 0.5 mg nebulized every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing; (17 micrograms/dose inhaler) 34 micrograms (2 puffs) every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing</td>
</tr>
</tbody>
</table>

- Short-acting bronchodilators include beta-2 agonists and anticholinergic bronchodilators. These medications are delivered either by nebulization or by metered-dose inhaler,[245] and both reduce symptoms of dyspnea; improve airflow, possibly by decreasing lung hyperinflation;[246] and are provided acutely to patients with an acute exacerbation as the initial treatment.[209] A systematic review did not find significant differences in FEV1 when short-acting bronchodilators were delivered by nebulizer as compared with metered-dose inhaler.[245] Severely dyspneic patients with low inspiratory flow rates may have difficulty achieving proper technique and medication delivery from the metered-dose inhaler devices; nebulizer treatment may be easier to use for such patients. Administration should be observed and a spacer should be used. There is insufficient evidence to determine whether metered-dose inhalers or the aerosol nebulizer technique is the optimal method of delivering bronchodilators to adults with COPD exacerbation who are receiving mechanical ventilation via endotracheal tube.[247]
Acute exacerbation of chronic obstructive pulmonary disease

Acute

» Beta-2 agonists are typically favored as first-line as they function more rapidly than anticholinergic bronchodilators. Initial therapy with beta-2 agonists may lead to a transient reduction in PaO2. If the initial dose of short-acting bronchodilator does not provide sufficient benefit, the frequency of dosing may be increased and an anticholinergic bronchodilator may be added. Nebulized ipratropium may be given in combination with nebulized albuterol. Ipratropium may be used in lieu of albuterol for patients developing significant adverse effects due to beta-2 agonist use. Levalbuterol also 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 (eg tachycardia/tachyarrythmia).

» It is not clear whether the combination of a beta-2 agonist plus an anticholinergic bronchodilator provides additional benefit. While there is no definitive evidence that the combination improves outcomes, patients may derive symptomatic benefit and additional bronchodilation because these agents work by different mechanisms. Combination therapy is generally recommended for patients who are not improving promptly on a beta-2 agonist alone.

» After clinical improvement, the time between doses may be increased as tolerated.

» Optimal dosing of bronchodilators in acute exacerbations of COPD is yet to be determined; however, guidelines generally recommend increasing the dose or frequency of administration. The doses recommended below are a guide only and local protocols should be consulted.

plus systemic corticosteroid

Treatment recommended for ALL patients in selected patient group

Primary options

» prednisone: 30-40 mg orally once daily for 5-7 days

OR
Acute exacerbation of chronic obstructive pulmonary disease

**Acute**

- **methylprednisolone**: 40-60 mg/day orally given once daily or in 2 divided doses for 5-7 days

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

The use of systemic corticosteroids for the treatment of acute exacerbation of COPD has been associated with greater early improvement in FEV1, improved oxygenation, faster recovery time, decreased duration of hospitalization, and decreased rate of treatment failure and relapsed disease. However, there is no evidence that the use of corticosteroids has effect on rates of mortality, and the benefits for people with acute exacerbations associated with respiratory failure and the need for mechanical ventilation are less clear.

Studies identifying benefit in the use of corticosteroids have used a range of dose amounts and treatment durations. Previous national and international guidelines recommended that patients receive 30 to 40 mg prednisone, or equivalent, for 7 to 14 days. It is not known whether tapering systemic corticosteroids provides clinical benefit apart from likely avoidance of adrenal insufficiency. One randomized controlled trial showed that 5 days’ treatment with 40 mg/day of prednisone was noninferior to 14 days’ treatment in regard to risk of exacerbations in the subsequent 6 months. This 5-day regimen is recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. The Department of Veterans’ Affairs recommends a similar dose of 30 to 40 mg/day of prednisone for 5 to 7 days. An equivalent oral dose of methylprednisolone may also be used. 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.

Systemic corticosteroids should be initiated after the first treatment of short-acting inhaled bronchodilators.
Acute exacerbation of chronic obstructive pulmonary disease

**Treatment**

### Acute

- Diabetes is common in patients with COPD, and the need for treatment of hyperglycemia is more frequently encountered when patients receive systemic corticosteroids.[198] [199]

- For patients able to take oral medications, intravenous corticosteroids do not appear to provide any significant benefit over those taken orally.[199] [201] [255] [256]

- The shortest duration of systemic corticosteroids that confers clinical benefit while minimizing adverse effects remains unclear.[202]

#### adjunct

**airway clearance techniques**

Treatment recommended for SOME patients in selected patient group

- Selected airway clearance techniques such as mechanical vibration and non-oscillating positive expiratory pressure 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,[257] but are not uniformly helpful.[208] Other clearance techniques such as manual chest wall percussion are also either not routinely helpful or may have detrimental effects.[258] [259] [260] There is no proven benefit of airway clearance techniques on long-term outcomes following COPD exacerbation, such as reduction in subsequent exacerbation risk.[257]

#### adjunct

**oxygen**

Treatment recommended for SOME patients in selected patient group

- Oxygen therapy is recommended for patients with acute exacerbations who are hypoxic (PaO2 <60 mmHg, SaO2 ≤90%). Oxygen is best administered in a controlled fashion via a high-flow Venturi mask to deliver 24% to 28% oxygen.[180] The goal of oxygen therapy is to increase PaO2 to ≥60 mmHg and SaO2 ≥90%.[12] [45] For patients with hypercarbia and more severe episodes, an ABG analysis is recommended 30 to 60 minutes after initiating oxygen therapy. 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.[261] Careful titration of supplemental oxygen even in the pre-
### Acute exacerbation of chronic obstructive pulmonary disease

#### Treatment

Hospital setting (e.g., en route to the hospital) is important to prevent worsening respiratory acidosis and may impact mortality.\[197\] Oxygen therapy may be discontinued when the patient is able to maintain PaO₂ ≥60 mmHg and/or SaO₂ ≥90% on room air.

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
- **doxycycline**: 100 mg orally twice daily
- **sulfamethoxazole/trimethoprim**: 160 mg orally twice daily
  - Dose refers to trimethoprim component.
- **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
- **cefuroxime sodium**: 750 mg intravenously every 8 hours
- **amoxicillin/clavulanate**: 875 mg orally twice daily
  - Dose refers to amoxicillin component.
- **clarithromycin**: 500 mg orally twice daily

The severity depends on patient's prior status and any changes to previous baseline investigation (based on symptoms, examination, lung function, ABG).
## Acute exacerbation of chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>Treatment</th>
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<tbody>
<tr>
<td><strong>Acute</strong></td>
</tr>
<tr>
<td>» Antibiotics should be given to patients with severe exacerbations requiring assisted ventilation, and those suspected of having a bacterial trigger for their acute exacerbations,[12][30][262] including in an acute exacerbation with increased sputum purulence, increased sputum volume, and/or worsening dyspnea.[1][176][194]</td>
</tr>
<tr>
<td>» It has been recommended that more narrow-spectrum antibiotics (e.g., amoxicillin, amoxicillin/clavulanate, doxycycline, tetracycline, second-generation cephalosporins, macrolide, trimethoprim/sulfamethoxazole) be considered for patients at less risk for a poor outcome and with an exacerbation of lesser severity.[194]</td>
</tr>
<tr>
<td>» It has been shown that short courses (e.g., 5 days) of antibiotics are equally effective as courses &gt;5 days for patients with mild to moderate exacerbations of COPD,[263][264] and the recommended length of therapy is usually 5 to 7 days.[1]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prevalent bacterial etiology (exacerbation of greater severity)</th>
<th>Adjunct broad-spectrum antibiotic</th>
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</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
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</table>

### Primary options
- **Levoﬂoxacin**: 500 mg orally once daily for 3-10 days, or 750 mg orally once daily for 5 days
  - OR
- **Ciproﬂoxacin**: 500 mg orally twice daily for 7-10 days
  - OR
- **Moxifloxacin**: 400 mg orally/intravenously once daily for 3-10 days
  - OR
- **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

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Acute exacerbation of chronic obstructive pulmonary disease

**Treatment**

**Acute**

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<th>Acute</th>
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<tr>
<td>Dose consists of 3 g of piperacillin and 0.375 g of tazobactam.</td>
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</table>

**OR**

- **vancomycin**: 500-1000 mg intravenously every 12 hours

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

- Antibiotics should be given to patients with severe exacerbations requiring assisted ventilation, and those suspected of having a bacterial trigger for their acute exacerbations,[1] [12] [30] [262] including in an acute exacerbation with increased sputum purulence, increased sputum volume, and/or worsening dyspnea.[1] [176] [194]

- It has been recommended that broad-spectrum antibiotics such as extended-spectrum beta-lactam combination drugs, fluoroquinolones, and vancomycin are reserved for patients at greater risk for a poor outcome, people with more severe baseline COPD, or patients with an episode of greater severity,[60] [194] including people who require hospitalization. Agents with activity against *Pseudomonas aeruginosa* are indicated for people at risk of this infection.[30]

- 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 history of frequent exacerbations, and patients hospitalized with COPD exacerbations or who require mechanical ventilation.[1] [30]

**respiratory insufficiency**

**adjunct**

**noninvasive positive-pressure ventilation**

Treatment recommended for SOME patients in selected patient group

- Severity depends on patient's prior status and any changes to previous baseline investigation (based on symptoms, examination, lung function, ABG). Use of accessory respiratory muscles, paradoxical respirations, cyanosis, new peripheral edema, hemodynamic instability,
Acute exacerbation of chronic obstructive pulmonary disease

**Treatment**

<table>
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<th>Acute</th>
<th>Treatment</th>
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<td>and worsened mental status (e.g., confusion, lethargy, coma) are important indicators of severity of exacerbation.[1]</td>
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<tr>
<td>» Respiratory failure is often seen in patients with severe acute exacerbations of COPD. The application of noninvasive positive-pressure ventilation (NPPV) 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] [173] [222] [223] [265] [266] [267]</td>
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<tr>
<td>» NPPV use should be considered for patients with one or more of the following: respiratory acidosis (PaCO2 ≥ 6.0 kPa or 45 mmHg and arterial pH ≤ 7.35); severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work or breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces; persistent hypoxemia despite supplemental oxygen therapy.[1]</td>
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<tr>
<td>» Improvements in patient's level of dyspnea and their physiologic state are typically seen within 1 to 4 hours.[268] However, NPPV is not successful for all patients, and clinicians should discuss the risks and benefits of invasive mechanical ventilation with patients receiving NPPV to determine their desired course of treatment.</td>
<td></td>
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<tr>
<td><strong>adjunct</strong></td>
<td>Invasive positive-pressure ventilation</td>
</tr>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td>» Severity depends on patient's prior status and any changes to previous baseline investigation (based on symptoms, examination, lung function, ABG). Use of accessory respiratory muscles, paradoxical respirations, cyanosis, new peripheral edema, hemodynamic instability, and worsened mental status (e.g., confusion, lethargy, coma) are important indicators of severity of exacerbation.[1] [45]</td>
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</table>
| » Noninvasive positive-pressure ventilation (NPPV) 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 NPPV, have impaired mental status or cardiovascular instability, are at high risk for aspiration, or have thick or copious secretions, or for whom NPPV cannot be appropriately applied (e.g., craniofacial trauma, recent
gastroesophageal surgery, anxiety disorder). [225]

» Physiologic criteria for invasive mechanical ventilation include the following: severe hypoxia, inability to tolerate NPPV or failure of NPPV, 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 without response to therapy, or severe ventricular or supraventricular arrhythmias.[1] [226]

» The risk for mortality is significant (11% to 49%) for people with severe disease in whom invasive mechanical ventilation is indicated.[12] [227] Complications of mechanical ventilation include ventilator-associated pneumonia and barotrauma.

» Weaning patients with severe COPD from mechanical ventilation can be difficult.[225] Use of NPPV to assist weaning from mechanical ventilation can reduce weaning failure and nosocomial pneumonia, and may reduce mortality.[224] [228]
Acute exacerbation of chronic obstructive pulmonary disease

**Treatment**

**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.\[269\] [270]

- 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 compliance and inhaler technique, supplemental oxygen, and maintenance of physical activity).\[233\] [234]

- Exercise training, particularly resistance training and transcutaneous electrical muscle stimulation initiated during hospitalization for COPD exacerbation are well tolerated and can prevent muscle function decline and hasten functional status recovery.\[235\] [236] [237]

- 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.\[238\] [240] [241] [242] [271] [272] [273] Comprehensive supervised pulmonary rehabilitation in the outpatient setting in the post-exacerbation period also decreases the risk for future hospitalization and may reduce mortality.\[233\] [241] [243] 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.

- Disease management programs can be helpful,\[232\] [274] [275] [276] 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.\[277\] 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.\[244\]
Acute exacerbation of chronic obstructive pulmonary disease

**TREATMENT**

<table>
<thead>
<tr>
<th>Ongoing</th>
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<tbody>
<tr>
<td>» 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. 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.</td>
</tr>
<tr>
<td>» 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. However, another randomized controlled trial demonstrated that telemonitoring integrated into existing clinical services did not reduce hospital admissions or improve patients’ quality of life.</td>
</tr>
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Recommendations

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.[300] 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 compliance with their medication regimens and that they have received appropriate vaccinations (e.g., influenza, pneumococcus).

Patient instructions

Patients often under-report symptoms of acute exacerbation.[301] 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.[302]

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.
Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<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>
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<tr>
<td>antibiotic-related diarrhea</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Antibiotic-associated colitis, which may be due to <em>Clostridium difficile</em>, 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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</table>

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.[291] 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.[292] Rehospitalization and/or mortality have been associated with lower FEV1, higher...
Acute exacerbation of chronic obstructive pulmonary disease

Follow up

PaCO₂, lower PaO₂, greater APACHE II score, lower BMI, older age, comorbidities, and low physical activity levels.\[227\] \[293\] \[294\] \[295\] \[296\] \[297\] \[298\] 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.\[299\]
Diagnostic guidelines

International

Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (http://goldcopd.org/gold-reports/) [1]
Published by: Global Initiative for Chronic Obstructive Lung Disease Last published: 2017

Veterans Affairs/Department of Defense clinical practice guideline: the management of chronic obstructive pulmonary disease (http://www.healthquality.va.gov/) [194]
Published by: US Department of Veterans Affairs and US Department of Defense Last published: 2014

Diagnosis and management of stable chronic obstructive pulmonary disease (http://www.acponline.org/clinical_information/guidelines/guidelines/) [195]
Published by: American College of Physicians; American College of Chest Physicians; American Thoracic Society; European Respiratory Society Last published: 2011

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (https://www.nice.org.uk/guidance/ng115) [196]
Published by: National Institute for Health and Care Excellence (UK) Last published: 2019
## Treatment guidelines

### International

<table>
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<tr>
<th>Guideline</th>
<th>Published by</th>
<th>Last published</th>
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<tbody>
<tr>
<td>Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (<a href="http://goldcopd.org/gold-reports/">http://goldcopd.org/gold-reports/</a>)</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
<td>2017</td>
</tr>
<tr>
<td>Diagnosis and management of stable chronic obstructive pulmonary disease (<a href="http://www.acponline.org/clinical_information/guidelines/guidelines/">http://www.acponline.org/clinical_information/guidelines/guidelines/</a>)</td>
<td>American College of Physicians; American College of Chest Physicians; American Thoracic Society; European Respiratory Society</td>
<td>2011</td>
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</tbody>
</table>
### International

**Screening for chronic obstructive pulmonary disease: U.S. Preventive Services Task Force recommendation statement** (https://jamanetwork.com/journals/jama/fullarticle/2510917)  [285]

*Published by:* US Preventive Services Task Force, Agency for Healthcare Research and Quality  
*Last published:* 2016


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


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

**Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines** (http://journal.publications.chestnet.org/article.aspx?articleid=1084262)  [288]

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

**Chronic cough due to chronic bronchitis: ACCP evidence-based clinical practice guidelines** (http://journal.publications.chestnet.org/article.aspx?articleid=1084244)  [289]

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


*Published by:* British Thoracic Society  
*Last published:* 2006


*Published by:* European Respiratory Society; European Society for Clinical Microbiology and Infectious Diseases  
*Last published:* 2011

**Chronic obstructive pulmonary disease in over 16s: diagnosis and management** (https://www.nice.org.uk/guidance/ng115)  [196]

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

**Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing** (https://www.nice.org.uk/guidance/ng114)  [290]

*Published by:* National Institute for Health and Care Excellence (UK)  
*Last published:* 2018
Key articles


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216. Grossman RF, Ambrusz ME, Fisher AC, et al. Levofloxacin 750 mg QD for five days versus amoxicillin/clavulanate 875 mg/125 mg BID for ten days for treatment of acute bacterial exacerbation of chronic...
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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

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Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

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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