Chronic obstructive pulmonary disease (COPD)
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<tr>
<td>− Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation that is not fully reversible.</td>
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<td>− Suspected in patients with a history of smoking, occupational and environmental risk factors, or a personal or family history of chronic lung disease.</td>
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<td>− Presents with progressive shortness of breath, wheeze, cough, and sputum production, including hemoptysis.</td>
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<td>− Diagnostic tests include pulmonary function tests, chest x-ray, chest computed tomography scan, oximetry, and arterial blood gas analysis.</td>
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<td>− Patients should be encouraged to stop smoking or occupational exposure and be vaccinated against viral influenza and Streptococcus pneumoniae.</td>
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<tr>
<td>− Treatment options include bronchodilators, inhaled corticosteroids, and systemic corticosteroids.</td>
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<td>− Long-term oxygen therapy improves survival in severe COPD.</td>
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**Definition**

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. It encompasses both emphysema and chronic bronchitis. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. It is primarily caused by cigarette smoking. Although COPD affects the lungs, it also has significant systemic consequences. Exacerbations and comorbidities are important contributors to the overall condition and prognosis in individual patients.[1]

**Epidemiology**

COPD is more common in older people, especially those ages 65 years and older. Associated mortality in women has more than doubled over the past 20 years and now matches that in men. The number of COPD cases in the US has increased by 41% since 1982, and COPD affects 1% to 3% of white women and 4% to 6% of white men. COPD is projected to be the third leading cause of death in the world by 2020.[1] This is because of the expanding epidemic of smoking and aging of the world population and reduced mortality from other causes of death such as cardiovascular disease.[1][5] A systematic review and meta-analysis has shown that the prevalence of COPD in adult offspring of people with COPD is greater than population-based estimates.[6]

**Etiology**

Tobacco smoking is by far the main risk factor for COPD. It is responsible for 40% to 70% of COPD cases and exerts its effect by causing an inflammatory response, cilia dysfunction, and oxidative injury. Air pollution and occupational exposure are other common etiologies. Oxidative stress and an imbalance in proteinases and antiproteinases are also important factors in the pathogenesis of COPD, especially in patients with alpha-1 antitrypsin deficiency, who have panacinar emphysema that usually presents at an early age.[1]

**Pathophysiology**

The hallmark of COPD is chronic inflammation that affects central airways, peripheral airways, lung parenchyma and alveoli, and pulmonary vasculature. The main components of these changes are narrowing and remodeling of airways, increased number of goblet cells, enlargement of mucus-secreting glands of the central airways, and, finally, subsequent vascular bed changes leading to pulmonary hypertension. This is thought to lead to the pathologic changes that define the clinical presentation.

Evidence suggests that the host response to inhaled stimuli generates the inflammatory reaction responsible for the changes in the airways, alveoli, and pulmonary blood vessels. Activated macrophages, neutrophils, and leukocytes are the core cells in this process. In contrast to asthma, eosinophils play no role in COPD, except for occasional acute exacerbations. However, a patient-level meta-analysis found that patients with COPD with lower blood eosinophil counts have more pneumonia events than do those with higher counts.[7]

In emphysema, which is a subtype of COPD, the final outcome of the inflammatory responses is elastin breakdown and subsequent loss of alveolar integrity.[8] In chronic bronchitis, another phenotype of COPD, these inflammatory changes lead to ciliary dysfunction and increased goblet cell size and number, which leads to the excessive mucus secretion. These changes are responsible for decreased airflow, hypersecretion, and chronic cough. In both conditions, changes are progressive and usually not reversible.
Increased airway resistance is the physiologic definition of COPD. Decreased elastic recoil, fibrotic changes in lung parenchyma, and luminal obstruction of airways by secretions all contribute to increased airways resistance. Expiratory flow limitation promotes hyperinflation. This finding, in addition to destruction of lung parenchyma, predisposes COPD patients to hypoxia, particularly during activity. Progressive hypoxia causes vascular smooth muscle thickening with subsequent pulmonary hypertension, which is a late development conveying a poor prognosis.\[9\] \[10\]
Primary prevention

Avoidance of tobacco exposure (both active and passive measures) and toxic fumes are of invaluable importance in primary prevention of COPD. All smokers should be offered interventions aimed at smoking cessation, including pharmacotherapy and counseling. Although smoking cessation may be associated with minor short-term adverse effects such as weight gain and constipation, its long-term benefits are unquestionable.[17] For disease due to occupational exposures, primary prevention is achieved by elimination or reduction of exposures in the workplace.

Screening

There are no data to show conclusively that screening spirometry is effective in directing management decisions or in improving COPD outcomes in patients who are identified before the development of significant symptoms.[24] However, if COPD is diagnosed at an early stage and risk factors are eliminated, the rate of decline in lung function will dramatically decrease. Treatment is much more efficacious in the early stages of disease.[25]

Screening can be done by asking about smoking history and environmental or occupational exposure. In high-risk populations a screening spirometry should be obtained to document airway obstruction. Some experts advocate conducting screening spirometry in all patients with findings compatible with emphysema on chest x-ray or computed tomography of the chest. Significant pulmonary dysfunction may be present in asymptomatic smokers.

Secondary prevention

Vaccination against viral influenza and *Streptococcus pneumoniae* is strongly recommended in all patients with cardiopulmonary diseases, including COPD.

Use of calcium and other medication may be necessary to prevent or treat osteoporosis in some patients, especially older women on long-term corticosteroid therapy. Bone density scans are done to evaluate progression of this condition.

There are conflicting data with regards to prophylactic antibiotic therapies. Prophylactic antibiotics, such as macrolides, may be considered for reducing the risk of acute exacerbation.[147] [148] While current guidelines do not yet advocate the use of prophylactic antibiotics, evidence from the MACRO study suggests that azithromycin reduces the risk of acute exacerbations in patients with COPD. However, when administered for 1 year, the most noted side effect was a decrement in hearing.[149] Azithromycin therapy is believed to be most effective in preventing acute exacerbation with a great efficacy in older patients and milder Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages. Little evidence of treatment benefit is seen in current smokers.[114]

Physical activity is recommended for all patients with COPD.[1]
Case history

Case history #1

A 66-year-old man with a smoking history of 1 pack per day for the past 47 years presents with progressive shortness of breath and chronic cough, productive of yellowish sputum, for the past 2 years. On examination he appears cachectic and in moderate respiratory distress, especially after walking to the examination room, and has pursed-lip breathing. His neck veins are mildly distended. Lung examination reveals a barrel chest and poor air entry bilaterally, with moderate inspiratory and expiratory wheezing. Heart and abdominal examination are within normal limits. Lower extremities exhibit scant pitting edema.

Case history #2

A 56-year-old woman with a history of smoking presents to her primary care physician with shortness of breath and cough for several days. Her symptoms began 3 days ago with rhinorrhea. She reports a chronic morning cough productive of white sputum, which has increased over the past 2 days. She has had similar episodes each winter for the past 4 years. She has smoked 1 to 2 packs of cigarettes per day for 40 years and continues to smoke. She denies hemoptysis, chills, or weight loss and has not received any relief from over-the-counter cough preparations.

Other presentations

Other presentations include weight loss, hemoptysis, cyanosis, and morning headaches secondary to hypercapnia. Physical examination may demonstrate hypoxia, use of accessory muscles, paradoxical rib movements, distant heart sounds, lower-extremity edema and hepatomegaly secondary to cor pulmonale, and asterixis secondary to hypercapnia. Patients may also present with signs and symptoms of COPD complications. These include severe shortness of breath, severely decreased air entry, and chest pain secondary to an acute COPD exacerbation or spontaneous pneumothorax.[2][3] Patients with COPD often have other comorbidities, including cardiovascular disease,[4] skeletal muscle dysfunction, metabolic syndrome and diabetes, osteoporosis, depression, lung cancer, gastroesophageal reflux disease, bronchiectasis, and obstructive sleep apnea.[1]

Step-by-step diagnostic approach

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

History

COPD has an insidious onset and usually presents in older people. A history of productive cough, wheezing, and shortness of breath, particularly with exercise, is typical. Patients may complain of fatigue as a result of disrupted sleep secondary to constant nocturnal cough and persistent hypoxia and hypercapnia. The patient's smoking history, occupational exposures, and any family history of lung disease should be determined.
Patients with COPD may also present with acute, severe shortness of breath, fever, and chest pain during acute infectious exacerbation. See our topic on Acute exacerbation of chronic obstructive pulmonary disease for further information.

**Physical exam**

Examination may show tachypnea, respiratory distress, use of accessory muscles, and intercostal retraction. Barrel chest is a common observation. There may be hyperresonance on percussion, and distant breath sounds and poor air movement on auscultation. Wheezing, coarse crackles, clubbing, and cyanosis, as well as signs of right-side heart failure (distended neck veins, loud P2, hepatomegaly, hepatojugular reflux, and lower-extremity edema), may be present. Occasionally patients may exhibit asterixis - loss of postural control in the outstretched arms (commonly known as a flap) caused by hypercapnia. This is due to impaired gas exchange in lung parenchyma, worsens with exercise, and is suggestive of respiratory failure.

**Initial tests**

Spirometry is the first test for diagnosis of COPD and for monitoring disease progress. Patients with COPD have a distinctive pattern seen on spirometry, with a reduced FEV1 and FEV1/FVC ratio. The presence of airflow limitation is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria as a postbronchodilator FEV1/FVC <0.70.[1] In cases where FVC may be hard to measure, FEV6 (forced expiratory volume at 6 seconds) can be used.[18] Chest x-ray (CXR) is rarely diagnostic but can help exclude other diagnoses. Pulse oximetry screens for hypoxia.

In addition to airflow limitation, the GOLD guidelines recognize the importance of exacerbations in affecting the natural course of COPD, and place emphasis on assessment of symptoms, risk factors for exacerbations, and comorbidities.[1]

The Modified British Medical Research Council (mMRC) questionnaire or the COPD Assessment Test (CAT) are recommended to assess symptoms. These can be found in the GOLD guidelines.[1]

The number of previously treated exacerbations (2 or more per year) is the best predictor of having another exacerbation. In addition to previous exacerbations, airflow limitation <50% is predictive of exacerbations.

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 mMRC or CAT scale.

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

**Other tests**

Detailed pulmonary function tests performed in specialist pulmonary function laboratories can measure diffusing capacity of the lung for carbon monoxide (DLCO), flow volume loops, and inspiratory capacity.
Chronic obstructive pulmonary disease (COPD)

**Diagnosis**

They are not used routinely but can be helpful in resolving diagnostic uncertainties and for preoperative assessment.[1]

In young patients (<45 years) with a family history or with rapidly progressing disease and lower lobe changes on imaging tests, alpha-1 antitrypsin level should be checked. The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once, especially in areas with high prevalence of alpha-1 antitrypsin deficiency.[19] This may aid in family screening and counseling.

Computed tomography scans show anatomic changes, but their usefulness in diagnosis is confined to patients considered for surgery and for ruling out other pathologies.[1]

Pulse oximetry should be used to assess all patients with clinical signs of respiratory failure or right heart failure. If peripheral arterial oxygen saturation is less than 92%, then arterial or capillary blood gases should be measured.[1]

Obstructive sleep apnea is associated with increased risk of death and hospitalization in patients with COPD.[20]

Exercise testing can be useful in patients with a disproportional degree of dyspnea.[21] It can be performed on a cycle or treadmill ergometer, or by a simple timed walking test (e.g., 6 minutes, or duration <6 minutes).[22] Exercise testing is also of use in selecting patients for rehabilitation. Respiratory muscle function may also be tested if dyspnea or hypercapnia are disproportionately increased with respect to FEV1, as well as in patients with poor nutrition and those with corticosteroid myopathy.[23]

In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum should be sent for culture.[1]

**Risk factors**

**Strong**

**cigarette smoking**

- Most important risk factor. It causes 40% to 70% of cases of COPD.[11]
- Elicits an inflammatory response and causes cilia dysfunction and oxidative injury.

**advanced age**

- The effect of age may be related to a longer period of cigarette smoking as well as the normal age-related loss of FEV1.

**genetic factors**

- Airway responsiveness to inhaled insults depends on genetic factors. Alpha-1 antitrypsin deficiency is a genetic disorder, mostly encountered in people of northern European ancestry, which causes panacinar emphysema in lower lobes at a young age.

**Weak**
white ancestry

- Despite high rates of smoking among black Americans and other racial and ethnic groups, COPD is more common in white people.

exposure to air pollution or occupational exposure

- Chronic exposure to dust, traffic exhaust fumes, and sulfur dioxide increases risk of COPD.

developmentally abnormal lung

- Frequent childhood infection may cause scarring of lungs, decrease elasticity, and increase risk for COPD.

male sex

- COPD is more common in men, but that is probably secondary to more smokers being male. However, there is a suggestion that women may be more susceptible than men to the effects of tobacco smoke. [12] [13] [14] [15]

low socioeconomic status

- The risk for developing COPD is increased in people with lower socioeconomic status. [16] However, this may reflect exposure to cigarette smoke, pollutants, or other factors.

History & examination factors

Key diagnostic factors

cough (common)

- Usually the initial symptom of COPD.
- Frequently a morning cough, but becomes constant as disease progresses.
- Usually productive, and sputum quality may change with exacerbations or superimposed infection.

shortness of breath (common)

- Initially with exercise but may progress to shortness of breath even at rest.
- Patients may have difficulty speaking in full sentences.

Other diagnostic factors

barrel chest (common)

- The anteroposterior diameter of the chest is increased.
- This suggests hyperinflation and air trapping secondary to incomplete expiration.

hyperresonance on percussion (common)

- Caused by hyperinflation and air trapping secondary to incomplete expiration.

distant breath sounds on auscultation (common)

- Caused by barrel chest, hyperinflation, and air trapping.

poor air movement on auscultation (common)

- Secondary to loss of lung elasticity and lung tissue breakdown.
Chronic obstructive pulmonary disease (COPD)

**Diagnosis**

**wheezing on auscultation (common)**
- A common finding in exacerbations. The current accepted descriptive word for a continuous musical lung sound.
- Is indicative of airway inflammation and resistance.

**coarse crackles (common)**
- A common finding in exacerbations. A discontinuous sound referring to mucus or sputum in airways.
- Indicative of airway inflammation and mucus oversecretion.

**tachypnea (uncommon)**
- An increased respiratory rate occurs to compensate for hypoxia and hypoventilation.
- May involve use of accessory muscles.

**asterixis (uncommon)**
- Loss of postural control in outstretched arms (commonly known as a flap) caused by hypercapnia.
- This is due to impaired gas exchange in lung parenchyma, worsens with exercise, and is suggestive of respiratory failure.

**distended neck veins (uncommon)**
- Occurs secondary to increased intrathoracic pressure and cor pulmonale.

**lower-extremity swelling (uncommon)**
- Suggests cor pulmonale and secondary pulmonary hypertension as a complication of advanced chronic lung disease.

**fatigue (uncommon)**
- Occurs because of disrupted sleep secondary to constant nocturnal cough and persistent hypoxia and hypercapnia.

**headache (uncommon)**
- May occur due to vasodilation caused by hypercapnia.

**cyanosis (uncommon)**
- Seen in the late stages of COPD, usually with hypoxia, hypercapnia, and cor pulmonale.

**loud P2 (uncommon)**
- Sign of advanced COPD.
- Indicates secondary pulmonary hypertension as a complication of cor pulmonale.

**hepatojugular reflux (uncommon)**
- Sign of advanced COPD complicated by cor pulmonale.

**hepatosplenomegaly (uncommon)**
- Sign of advanced COPD complicated by cor pulmonale.

**clubbing (uncommon)**
Chronic obstructive pulmonary disease (COPD)

• COPD itself does not cause clubbing, but if tobacco exposure in COPD patients leads to lung cancer and/or bronchiectasis, then clubbing may occur in COPD. Clubbing is usually not present until significant impairment of lung function has occurred.

Diagnostic tests

1st test to order

<table>
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<tr>
<th>Test</th>
<th>Result</th>
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<tr>
<td>spirometry</td>
<td>COPD is classified based on the patient’s FEV1 and its percentage of the predicted FEV1. In cases where FVC may be hard to measure, FEV6 (forced expiratory volume at 6 seconds) can be used.[18] FeV1/FVC ratio &lt;0.70; total absence of reversibility is neither required nor the most typical result</td>
</tr>
<tr>
<td>pulse oximetry</td>
<td>Checked as part of vital signs on acute presentation. A good pulse wave should be picked up by the device. In patients with chronic disease, an oxygen saturation of 88% to 90% may be acceptable. If &lt;92% arterial or capillary blood gases should be checked.[1] low oxygen saturation</td>
</tr>
<tr>
<td>ABG</td>
<td>Checked in patients who are acutely sick, especially if they have an abnormal pulse oximetry reading. Should also be performed in stable patients with FEV1 &lt;35% predicted or with clinical signs suggestive of respiratory failure, or if peripheral arterial oxygen saturation is &lt;92%. Hypercapnia, hypoxia, and respiratory acidosis are signs of impending respiratory failure and possible need for intubation. PaCO₂ &gt;50 mmHg and/or PaO₂ of &lt;60 mmHg suggests respiratory insufficiency</td>
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<tr>
<td>CXR</td>
<td>Seldom diagnostic, but useful in ruling out other pathologies. Increased anteroposterior ratio, flattened diaphragm, increased intercostal spaces, and hyperlucent lungs may be seen. May also demonstrate complications of COPD, such as pneumonia and pneumothorax. hyperinflation</td>
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<tr>
<td>CBC</td>
<td>This test may be considered to assess severity of an exacerbation and may show polycythemia (hematocrit &gt;55%), anemia, and leukocytosis.[1] elevated hematocrit, possible increased WBC count</td>
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<tr>
<td>ECG</td>
<td>Risk factors for COPD are similar to those for ischemic heart disease, so comorbidity is common. signs of right ventricular hypertrophy, arrhythmia, ischemia</td>
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### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tr>
<td><strong>pulmonary function tests</strong></td>
<td>obstructive pattern, decreased DLCO</td>
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<tr>
<td>- Useful for resolving diagnostic uncertainties and for preoperative assessment.[1] Requires specialist laboratory facilities.</td>
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<td>- Decreased diffusing capacity of the lung for carbon monoxide (DLCO) is supportive of emphysema over chronic bronchitis.</td>
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<td><strong>chest CT scan</strong></td>
<td>hyperinflation</td>
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<tr>
<td>- Provides better visualization of type and distribution of lung tissue damage and bulla formation than CXR. [Fig-3]</td>
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<tr>
<td>- In contrast to smoking-related COPD, alpha-1 antitrypsin deficiency mainly affects lower fields.</td>
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<tr>
<td>- Useful in excluding other underlying pulmonary disease and in preoperative assessment.</td>
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<td><strong>sputum culture</strong></td>
<td>infecting organism</td>
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<tr>
<td>- In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum should be sent for culture.[1]</td>
<td></td>
</tr>
<tr>
<td><strong>alpha-1 antitrypsin level</strong></td>
<td>should be normal in patients with COPD</td>
</tr>
<tr>
<td>- Low level in patients with alpha-1 antitrypsin deficiency. Test is done if there is high suspicion for alpha-1 antitrypsin deficiency, such as a positive family history and atypical COPD cases (young patients and nonsmokers). The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once, especially in areas with high prevalence of alpha-1 antitrypsin deficiency.[19]</td>
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<td><strong>exercise testing</strong></td>
<td>poor exercise performance or exertional hypoxemia is suggestive of advanced disease</td>
</tr>
<tr>
<td>- Can be of value in patients with a disproportional degree of dyspnea compared with spirometry.[21] It can be performed on a cycle or treadmill ergometer, or by a simple timed walking test (e.g., 6 minutes, or duration &lt;6 minutes).[22] Exercise testing is of use in selecting patients for rehabilitation.</td>
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<tr>
<td><strong>sleep study</strong></td>
<td>elevated apnea-hypopnea index and/or nocturnal hypoxemia</td>
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<tr>
<td>- Obstructive sleep apnea, a common finding in patients with COPD, is associated with increased risk of death and hospitalization in patients with COPD.[20]</td>
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<tr>
<td><strong>respiratory muscle function</strong></td>
<td>reduced maximal inspiratory pressure</td>
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<tr>
<td>- Respiratory muscle function may be tested if dyspnea or hypercapnia are disproportionately increased with respect to FEV1, as well as in patients with poor nutrition and those with corticosteroid myopathy.[23]</td>
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## Differential diagnosis

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<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
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<tr>
<td>Asthma</td>
<td>• Onset of asthma is usually in early life. A personal or family history of allergy, rhinitis, and eczema is often present. There is daily variability in symptoms, and patients have overt wheezing that usually rapidly responds to bronchodilators. Cough variant asthma mimics many features of COPD.</td>
<td>• Pulmonary function tests (PFTs) show reversibility with bronchodilators and no decrease in diffusing capacity of the lung for carbon monoxide (DLCO). Sputum or blood eosinophilia is suggestive of asthma.</td>
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<td>Congestive heart failure</td>
<td>• Usually a history of cardiovascular diseases is present. Patients report symptoms of orthopnea, and fine bibasilar inspiratory crackles may be heard on auscultation.</td>
<td>• B-type natriuretic peptide levels are usually elevated, and CXR reveals increased pulmonary vascular congestion. Echocardiogram may confirm the diagnosis.</td>
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<td>Bronchiectasis</td>
<td>• There may be a history of recurrent infection in childhood. Large volume of purulent sputum is usually present. Coarse crackles may be heard on auscultation. History of pertussis or tuberculosis is a clue to diagnosis.</td>
<td>• Chest CT reveals bronchial dilation and bronchial wall thickening.</td>
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<td>Tuberculosis</td>
<td>• A history of fever, night sweats, weight loss, and chronic productive cough is usually present. Tuberculosis is more common in people living in or originating from endemic areas.</td>
<td>• The diagnosis requires microbiologic confirmation. Infiltrates, fibrosis, or granuloma seen on CXR or chest CT may suggest tuberculosis. Patients usually have positive skin test for tuberculosis.</td>
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<tr>
<td>Bronchiolitis</td>
<td>• Bronchiolitis may affect patients at younger ages. The patient may have a history of connective tissue disorders, especially rheumatoid arthritis, or fume exposure. Some cases are postinfectious.</td>
<td>• PFTs in bronchiolitis can present with obstructive, restrictive, or mixed pattern. CXR shows hyperinflation. High-resolution chest CT may show diffuse, small, centrilobular nodular opacities, but is rarely done in children due to radiation risk.</td>
</tr>
<tr>
<td>Upper airway dysfunction</td>
<td>• Can affect patients of any age. History of prior trauma</td>
<td>• The flow-volume curve in pulmonary function testing</td>
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### Chronic obstructive pulmonary disease (COPD)

#### Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
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<td></td>
<td>or intubation is very helpful. Lung examination is usually normal, but signs of upper airway restriction, such as wheezing and stridor, may be present. Patients may have voice hoarseness if vocal cords are involved.</td>
<td>may reveal a characteristic expiratory or inspiratory plateau, or both. Diagnosis is confirmed by direct visualization of the affected airway by endoscopy.</td>
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<tr>
<td>Chronic sinusitis/postnasal drip</td>
<td>• Chronic sinusitis/rhinitis is a very common cause of chronic cough. Patients may complain of sinus pressure, rhinorrhea, nonproductive cough, and/or headache.</td>
<td>• CT of sinuses and/or empiric trial of antihistamines are commonly utilized to aid in diagnosis.</td>
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<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
<td>• Patients with GERD often have dyspepsia and frequent belching, and can have a chronic cough that worsens at night when supine.</td>
<td>• Diagnosis is usually based on response to empiric therapy with proton-pump inhibitors.</td>
</tr>
<tr>
<td>ACE inhibitor-induced chronic cough</td>
<td>• ACE inhibitors can cause chronic cough; however, the cough is usually nonproductive.</td>
<td>• Diagnosis is usually based on improvement of symptoms after empiric cessation of ACE inhibitor.</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>• Patients may have weight loss, night sweats, hemoptysis, and/or chest or back pain.</td>
<td>• Radiography is important in the assessment for lung cancer. Bronchoscopy may be necessary to evaluate for endobronchial cancer if suspicion is high.</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

**Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[1]**

Classification of severity of airflow limitation in COPD:

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 $\geq 80\%$ predicted
- **GOLD 2 - moderate**: $50\% \leq$ FEV1 $<80\%$ predicted
- **GOLD 3 - severe**: $30\% \leq$ 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. These can be found in the GOLD guidelines.[1]

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

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

The ultimate goals of treatment of COPD are to prevent and control symptoms, to reduce the severity and number of exacerbations, to improve respiratory capacity for increased exercise tolerance, and to reduce mortality.[27] There is a stepwise approach to therapy, but it is important to remember that treatment should be individualized for general health status and comorbid conditions.

The therapeutic approach involves reducing risk factor exposure, appropriate assessment of disease, patient education, pharmacologic and nonpharmacologic management of stable COPD, and prevention and treatment of acute COPD exacerbations.

Continuous assessment and monitoring of disease

Ongoing monitoring and assessment in COPD ensures that the goals of treatment are being met. Quality of life and patients' sense of wellbeing will improve, and hospital admissions will be significantly decreased in cases where self- or professional monitoring of disease is being utilized.[28] Such assessment of the medical history should include:

Exposure to risk factors and preventive measures:

- Tobacco smoke
- Occupational exposures (fumes, dust, etc.)
- Influenza and pneumococcal vaccination.

Disease progression and development of complications:

- Decline in exercise tolerance
- Increased symptoms
- Worsened sleep quality
- Missed work or other activities.

Pharmacotherapy and other medical treatment:

- How often rescue inhaler is used
- Any new medicines
- Compliance with medical regimen
- Ability to use inhalers properly
- Adverse effects.

Exacerbation history:

- Urgent care or emergency room visits
- Recent oral corticosteroid bursts
- Frequency, severity, and likely causes of exacerbations should be evaluated.

Comorbidities:

- Assessment of coexisting medical problems (e.g., heart failure).
In addition, objective assessment of lung function should be obtained yearly or more frequently if there is a substantial increase in symptoms.

Integrated disease management (IDM) in which several healthcare providers (physical therapist, pulmonologist, nurse, etc.) worked together with patients has been shown to improve quality of life and decrease hospital admissions.[29]

**Acute exacerbations**

An exacerbation of COPD is defined as an event characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations and is acute in onset. See our topic on Acute exacerbation of chronic obstructive pulmonary disease for further information.

**Chronic management: stepwise therapy according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) class**

GOLD guidelines[27] recommend a stepwise approach to pharmacologic therapy:

- For group A patients (few symptoms and low risk of exacerbations), a bronchodilator is offered first-line. This can be either a short- or a long-acting bronchodilator. This should be continued if symptomatic benefit is documented.
- For group B patients (more symptoms and low risk of exacerbations), a long-acting bronchodilator should be offered first-line. If the patient has persistent symptoms when taking one long-acting bronchodilator, then the use of two bronchodilators is recommended. For patients with severe breathlessness, initial treatment with two bronchodilators may be warranted.
- For group C patients (few symptoms but higher risk of exacerbations), first-line treatment should be a long-acting bronchodilator, and GOLD recommends starting a long-acting muscarinic antagonist (LAMA) in this group. Patients who experience further exacerbations may benefit from adding a second long-acting bronchodilator (long-acting beta-2-agonist [LABA] or LAMA) or using a combination of a LABA and an inhaled corticosteroid (ICS). GOLD recommends a LABA/LAMA combination over LABA/ICS, as ICS increases the risk of developing pneumonia in some patients.
- For group D patients (more symptoms and high risk of exacerbations), GOLD recommends starting therapy with a LABA/LAMA combination. If patients experience further exacerbations when on LABA/LAMA, they can either try escalation to LABA/LAMA/ICS, or they can switch to LABA/ICS. If patients treated with LABA/LAMA/ICS still have exacerbations, then additional options include adding roflumilast, or a macrolide, or stopping the ICS.

All patients are candidates for education, vaccination, and smoking cessation interventions.

**Bronchodilator therapy options**

Beta agonists are widely used in the treatment of COPD. They increase intracellular cAMP, leading to respiratory smooth muscle relaxation and reduced airway resistance. They are available as short-acting and long-acting preparations. Short-acting beta-2 agonists improve lung function and breathlessness and quality of life. These agents can be used as rescue therapy when the patient is using long-acting beta-2 agonist therapy.[30] LABAs improve lung function, breathlessness, exacerbation rate, and number of hospitalizations, but do not affect mortality or rate of decline of lung function.[27]

A muscarinic antagonist is a type of anticholinergic agent that acts as a bronchodilator by blocking the cholinergic receptors on the respiratory smooth muscle. This causes muscle relaxation and reduces airflow limitation. Inhaled muscarinic antagonists are available as both short- and long-acting...
Chronic obstructive pulmonary disease (COPD)

Tiotropium, a LAMA, has been shown to reduce risk of exacerbation versus placebo or other maintenance treatments.[31] Newer LAMAs, such as aclidinium, glycopyrrolate, and umeclidinium, have at least comparable efficacy to tiotropium, in terms of change from baseline in trough forced expiratory volume in 1 second (FEV1), transitional dyspnea index focal score, St George's Respiratory Questionnaire score, and rescue medication use.[32] There is a suggestion of increased cardiovascular-related mortality in some studies of patients taking short-acting muscarinic antagonists and in some studies of patients taking LAMAs.[33] [34] A population-based cohort study found that older men with COPD newly started on LAMAs are at increased risk of urinary tract infections.[35]

Beta agonists and muscarinic antagonists, therefore, provide bronchodilator effects through different pathways. Their combination may provide a better therapeutic effect without increasing the adverse effects of each class.[36] [37] [38] [39] Compared to LABA/ICS, a LABA/LAMA combination has fewer exacerbations, a larger improvement of FEV1, a lower risk of pneumonia, and more frequent improvement in quality of life.[40] A systematic review and network meta-analysis found that all LABA/LAMA fixed-dose combinations had a similar efficacy and safety.[41]

In cases of stable COPD, if the decision is made to use single-agent therapy, LAMA may be superior to LABA agents.[36] Clinical trials have shown that LAMA have a greater effect on reducing rates of exacerbations compared with LABA.[42] [43] The long-term safety of LAMA was demonstrated in the UPLIFT trial.[44] As outlined above, GOLD makes recommendations on the initial agent based on the patient’s risk group (A, B, C, or D).[27]

Theophylline (a methylxanthine agent) is a bronchodilator that acts by increasing cAMP and subsequent respiratory smooth muscle relaxation. It is not commonly used because of limited potency, narrow therapeutic window, high-risk profile, and frequent drug-drug interactions. Theophylline is indicated for persistent symptoms if inhaled therapy is insufficient to relieve airflow obstruction. Theophylline has modest effects on lung function in moderate to severe COPD.[45]

Umeclidinium/vilanterol is a LABA/LAMA approved for use in COPD.[46] Glycopyrrolate/formoterol fumarate is another LABA/LAMA combination approved for COPD patients,[47] as is indacaterol/glycopyrrolate.[48] [49] This once-daily inhaler showed superior efficacy compared with glycopyrrolate plus tiotropium in patients with moderate to severe COPD,[50] and compared with salmeterol/fluticasone in preventing COPD exacerbation.[51]

Inhaled corticosteroids

Inhaled corticosteroids are indicated in patients with advanced stages of COPD who suffer from frequent exacerbations.[52] They should be added to the patient’s existing bronchodilator therapy and should not be used as monotherapy.[27] Inhaled corticosteroids are believed to be effective because of their anti-inflammatory effects. Long-term inhaled corticosteroid use reduces the need to use rescue therapy and reduces exacerbations, and may also decrease mortality.[53] [54] Several studies have pointed to an increased risk of pneumonia in COPD patients taking inhaled corticosteroids.[55] This risk is slightly higher for fluticasone in comparison with budesonide.[56] A systematic review and meta-analysis found that, despite a significant increase in unadjusted risk of pneumonia associated with use of inhaled corticosteroids, pneumonia fatality and overall mortality were not increased in randomized controlled trials and were decreased in observational studies.[57] Therefore, an individualized treatment approach that assesses a patient’s risk of pneumonia versus the benefit of decreased exacerbations should be implemented.[55] [58] [59] Concern is also raised with regards to increased risk of tuberculosis and influenza in adult patients with COPD who are on inhaled corticosteroid therapy.[60]
According to the GOLD guideline, inhaled corticosteroids are not recommended as first-line therapy in any of the patient groups A to D. They are only recommended as part of escalation of therapy if patients continue to experience exacerbations despite taking a long-acting bronchodilator.[27]

**Phosphodiesterase-4 inhibitors**

Roflumilast is an oral phosphodiesterase-4 inhibitor that may reduce exacerbations in group D patients at risk for frequent exacerbations when not adequately controlled by long-acting bronchodilators.[27] This agent offers benefit in improving lung function and reducing the likelihood of exacerbations. However, it has little impact on quality of life or symptoms.[61]

**Combined bronchodilator and corticosteroid preparations**

A combination preparation of long-acting bronchodilator and inhaled corticosteroid may be used for patients who require both these agents. This is convenient and may help with compliance in some patients. The choice of therapy in this class is based on availability and individual response and preference.[62] Combination therapy with inhaled corticosteroid and a long-acting beta agonist is superior to use of either agent alone.[63] [64] The combination may be provided in separate inhalers or a combination inhaler.

Multiple studies support triple therapy with LABA/LAMA/ICS as being superior to single- or double-agent therapy with LABA/LAMA or LABA/ICS regarding rate of moderate to severe COPD exacerbations[65] [66] [67] [68] and rate of hospitalization.[69] [70]

**Patient education and self-management**

All patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Their expectation of the disease, treatment, and prognosis should be realistic. It is important to remember that no medication has been shown to modify the long-term decline in lung function, and the primary goal of pharmacotherapy is to control symptoms and prevent complications.

One Cochrane review found that self-management interventions that include an action plan for acute exacerbations of COPD are associated with improvements in health-related quality of life and fewer admissions to the hospital for respiratory problems. An exploratory analysis found a small, but significantly higher, respiratory-related mortality rate for self-management compared to usual care, although no excess risk of all-cause mortality was seen.[71]

One randomized controlled trial found that a telephone health coaching intervention to promote behavior change in patients with mild COPD in primary care led to improvements in self-management activities, but did not improve health-related quality of life.[72]

Physical activity is recommended for all patients with COPD.[27] One systematic review and meta-analysis of randomized controlled trials found that exercise training on its own can improve physical activity in COPD, and greater improvements can be made with the addition of physical activity counseling.[73] Another systematic review and meta-analysis found that a combination of aerobic exercise and strength training was more effective than strength training or endurance training alone in increasing the 6-minute walking distance.[74]

**Smoking cessation and vaccination**

Smoking cessation should be encouraged in all patients, in addition to guidance on avoiding occupational or environmental tobacco smoke exposures.
Usual smoking cessation programs include counseling, group meetings, and drug therapy. Some patients may need frequent referrals to achieve success. Smoking cessation significantly reduces the rate of progression of COPD and risk of malignancies. It also reduces risk of coronary and cerebrovascular diseases. Smoking cessation that includes pharmacotherapy and intensive counseling has a higher success rate and is cost effective in COPD, with low costs per quality-adjusted life year.

Patients should be vaccinated against influenza virus and *Streptococcus pneumoniae*. Vaccination against influenza is associated with fewer exacerbations of COPD.

**Mucolytics**

Patients with the chronic bronchitis phenotype of COPD often produce thick sputum on a frequent basis. Mucolytic agents are not associated with an increase in adverse effects and may be beneficial during exacerbations of COPD. They result in a small reduction in the frequency of acute exacerbations, but do not improve lung function or quality of life. Mucolytic agents may be most beneficial for patients not on inhaled corticosteroids. The use of positive expiratory pressure (PEP) therapy to clear secretions during acute exacerbations has been found to improve subjective feelings of breathlessness but was not associated with decreased hospitalizations or rate of exacerbations.

**Pulmonary rehabilitation**

Pulmonary rehabilitation should be initiated for patients who remain symptomatic despite bronchodilator therapy and is recommended to start early in the course of the disease, when they start feeling shortness of breath with regular activity and walking on a level surface. Its effect is beneficial in improving exercise capacity and quality of life. It also decreases the depression and anxiety related to this disease, and reduces hospitalization in COPD patients. The benefit appears to subside after termination of the course unless patients follow a home exercise schedule. Benefits of home- or community-based pulmonary rehabilitation on respiratory symptoms and quality of life in patients with COPD could match those of the hospital-based rehabilitation programs. Although pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent, it is important to remember that early progressive exercise rehabilitation beyond current standard physical therapy practice during hospital admission for COPD is not recommended and could be associated with a higher 12-month mortality. There is evidence to support starting pulmonary rehabilitation within 1 month of an acute exacerbation.

GOLD guidelines recommend pulmonary rehabilitation for patient groups B to D.

**Oxygen therapy**

GOLD guidelines recommend long-term oxygen therapy in stable patients who have:

- \( \text{PaO}_2 \leq 7.3 \text{ kPa (55 mmHg)} \) or \( \text{SaO}_2 \leq 88\% \), with or without hypercapnia confirmed twice over a 3-week period; or
- \( \text{PaO}_2 \) between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or \( \text{SaO}_2 \) of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).

Oxygen therapy helps minimize pulmonary hypertension by decreasing pulmonary artery pressure, and improves exercise tolerance and quality of life. It has been shown to improve survival.
Chronic obstructive pulmonary disease (COPD) Treatment

Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg).[27] These patients usually have a saturation of <92% in room air at sea level. If in doubt, patients could undergo testing to be evaluated for their predicted PaO₂ during flight.

There is some evidence that oxygen can relieve breathlessness when given during exercise to mildly hypoxemic and nonhypoxemic people with COPD who do not otherwise qualify for home oxygen therapy.[93]

Surgery

Surgical interventions (bullectomy, lung volume reduction surgery,[94] [95] and lung transplant) are the last step in the management of COPD. They are used to improve lung dynamics, exercise adherence, and quality of life.[96] Endobronchial valve insertion can produce clinically meaningful improvements in appropriately selected COPD patients.[97]

Criteria for referral for lung transplantation include:[98]

- Progressive disease, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy.
- Patient is not a candidate for endoscopic or surgical lung volume reduction surgery (LVRS). Simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate.
- Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index of 5 to 6.
- PaCO₂ >50 mmHg or 6.6 kPa and/or PaO₂ <60 mmHg or 8 kPa.
- FEV1 <25% predicted.

Palliative care

For some patients with very advanced end-stage COPD, palliative care and hospice admission should be considered. Patient and family should be well educated about the process, and it is suggested that discussions should be held early in the course of the disease before acute respiratory failure develops.[99] One study has suggested that low doses of an opioid analgesic and a benzodiazepine are safe and are not associated with increased hospital admissions or mortality.[100]

One Cochrane review concluded that there is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD.[101]

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.
### Acute Treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Symptoms and Risk of Exacerbations</th>
<th>1st</th>
<th>2nd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong>: few symptoms and low risk of exacerbations</td>
<td>short- or long-acting bronchodilator</td>
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<td></td>
<td>plus patient education and vaccination</td>
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<td></td>
<td>plus smoking cessation</td>
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<td></td>
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<tr>
<td><strong>B</strong>: more symptoms and low risk of exacerbations</td>
<td>long-acting bronchodilator</td>
<td>dual long-acting bronchodilator therapy</td>
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<td></td>
<td>plus short-acting bronchodilator as required</td>
<td>plus short-acting bronchodilator as required</td>
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<td></td>
<td>plus patient education and vaccination</td>
<td>plus patient education and vaccination</td>
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<td>plus smoking cessation</td>
<td>plus smoking cessation</td>
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<td></td>
<td>plus pulmonary rehabilitation</td>
<td>plus pulmonary rehabilitation</td>
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<td></td>
<td>adjunct long-term oxygen therapy</td>
<td>adjunct long-term oxygen therapy</td>
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</table>

**Group C**: few symptoms but higher risk of exacerbations

<table>
<thead>
<tr>
<th>1st</th>
<th>2nd</th>
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<tbody>
<tr>
<td>long-acting bronchodilator</td>
<td>dual long-acting bronchodilator therapy</td>
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<tr>
<td>plus short-acting bronchodilator as required</td>
<td>plus short-acting bronchodilator as required</td>
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<tr>
<td>plus patient education and vaccination</td>
<td>plus patient education and vaccination</td>
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<tr>
<td>plus smoking cessation</td>
<td>plus smoking cessation</td>
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<tr>
<td>plus pulmonary rehabilitation</td>
<td>plus pulmonary rehabilitation</td>
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<tr>
<td>adjunct theophylline</td>
<td>adjunct long-term oxygen therapy</td>
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</tbody>
</table>

adjunct long-term oxygen therapy
### Chronic obstructive pulmonary disease (COPD) Treatment

#### Acute

<table>
<thead>
<tr>
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<tr>
<td>adjunct</td>
<td>theophylline</td>
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<td>adjunct</td>
<td>long-term oxygen therapy</td>
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<tr>
<td>3rd</td>
<td>long-acting beta-2 agonist plus inhaled corticosteroid</td>
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<td>plus</td>
<td>short-acting bronchodilator as required</td>
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<tr>
<td>plus</td>
<td>patient education and vaccination</td>
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<td>plus</td>
<td>smoking cessation</td>
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<td>plus</td>
<td>pulmonary rehabilitation</td>
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<td>theophylline</td>
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<td>long-term oxygen therapy</td>
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#### group D: more symptoms and high risk of exacerbations

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<tr>
<td>1st</td>
<td>dual long-acting bronchodilator therapy</td>
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<td>plus</td>
<td>short-acting bronchodilator as required</td>
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<td>plus</td>
<td>patient education and vaccination</td>
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<td>plus</td>
<td>smoking cessation</td>
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<td>plus</td>
<td>pulmonary rehabilitation</td>
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<td>adjunct</td>
<td>theophylline</td>
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<td>adjunct</td>
<td>long-term oxygen therapy</td>
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<tr>
<td>adjunct</td>
<td>surgical interventions</td>
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<tr>
<td>adjunct</td>
<td>palliative care</td>
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<tr>
<td>2nd</td>
<td>triple therapy: long-acting beta-2 agonist (LABA) plus long-acting muscarinic antagonist (LAMA) plus inhaled corticosteroid (ICS)</td>
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<tr>
<td>plus</td>
<td>short-acting bronchodilator as required</td>
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<tr>
<td>plus</td>
<td>patient education and vaccination</td>
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<td>plus</td>
<td>smoking cessation</td>
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<td>plus</td>
<td>pulmonary rehabilitation</td>
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<td>adjunct</td>
<td>theophylline</td>
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<td>adjunct</td>
<td>phosphodiesterase-4 inhibitor</td>
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<td>macrolide antibiotic</td>
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<td>adjunct</td>
<td>long-term oxygen therapy</td>
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<tr>
<td>adjunct</td>
<td>surgical interventions</td>
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### Acute Treatment

<table>
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<tr>
<th>Adjunct</th>
<th>Description</th>
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<td>Palliative care</td>
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<tr>
<td>2nd long-acting beta-2 agonist (LABA) plus inhaled corticosteroid (ICS)</td>
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<tr>
<td>Short-acting bronchodilator as required</td>
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<tr>
<td>Patient education and vaccination</td>
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<td>Smoking cessation</td>
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<td>Theophylline</td>
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<td>Surgical interventions</td>
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<tr>
<td>Palliative care</td>
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Treatment options

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### Acute

**group A: few symptoms and low risk of exacerbations**

<table>
<thead>
<tr>
<th>1st short- or long-acting bronchodilator</th>
<th>Primary options</th>
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<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» albuterol inhaled: (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required</td>
<td>OR</td>
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<tr>
<td>» levalbuterol inhaled: (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required</td>
<td>OR</td>
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<tr>
<td>» ipratropium bromide inhaled: (17 micrograms/dose inhaler) 34 micrograms (2 puffs) up to four times a day when required, maximum 204 micrograms/day</td>
<td>OR</td>
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<tr>
<td>» salmeterol inhaled: (50 micrograms/dose inhaler) 50 micrograms (1 puff) twice daily</td>
<td>OR</td>
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<tr>
<td>» indacaterol inhaled: (75 microgram/capsule inhaler) 75 micrograms (1 capsule) once daily</td>
<td>OR</td>
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<tr>
<td>» arformoterol inhaled: 15 micrograms nebulized twice daily</td>
<td>OR</td>
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<tr>
<td>» olodaterol inhaled: (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily</td>
<td>OR</td>
</tr>
<tr>
<td>» tiotropium inhaled: (18 micrograms/capsule inhaler) 18 micrograms (1 capsule) once daily; (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily</td>
<td>OR</td>
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</table>
Chronic obstructive pulmonary disease (COPD)

**TREATMENT**

**Acute**

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<tbody>
<tr>
<td></td>
<td>» umeclidinium inhaled: (62.5 micrograms/dose inhaler) 62.5 micrograms (1 puff) once daily</td>
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<td>OR</td>
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<td></td>
<td>» aclidinium bromide inhaled: (400 micrograms/dose inhaler) 400 micrograms (1 puff) twice daily</td>
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<td>OR</td>
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<tr>
<td></td>
<td>» glycopyrrolate inhaled: (15.6 micrograms/capsule inhaler) 15.6 micrograms (1 capsule) twice daily; (25 micrograms/vial nebulizer inhalation solution) 25 micrograms nebulized twice daily using Magnair® nebulizer device</td>
<td></td>
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</tbody>
</table>

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that all group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator.[27]

The effect of the bronchodilator should be evaluated. Depending on the response, it should be continued or stopped or another class of bronchodilator should be tried.[27]

Short-acting bronchodilators provide symptomatic relief.

Failure to respond to short-acting bronchodilator may signify an acute exacerbation.

Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[102] [103]

Short-acting drugs include albuterol, levalbuterol, and ipratropium.

Long-acting drugs include salmeterol, indacaterol, arformoterol, olodaterol, tiotropium, umeclidinium, aclidinium, and glycopyrrolate.

**plus patient education and vaccination**

Treatment recommended for ALL patients in selected patient group

Influenza and pneumococcal vaccination should be offered to every COPD patient.[27] Influenza vaccine is given annually. Pneumococcal vaccine should be given to COPD patients older than 65 years of age and to younger patients with significant comorbid...
Chronic obstructive pulmonary disease (COPD)  

**Treatment**

**Acute**

conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%.[104]

» Patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Physical activity is recommended for all patients with COPD.[27]

» Discussions should be held early in the course of the disease, before acute respiratory failure develops, about the possible need for and benefits of palliative care in the future.[99]

**plus smoking cessation**

Treatment recommended for ALL patients in selected patient group

» All patients should be strongly recommended not to start smoking, or to stop if they are current smokers. Smoking cessation is a primary goal in management of COPD.

» Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate nonpharmacologic therapies, should be used.

**group B: more symptoms and low risk of exacerbations**

<table>
<thead>
<tr>
<th>1st</th>
<th>long-acting bronchodilator</th>
</tr>
</thead>
</table>

**Primary options**

» salmeterol inhaled: (50 micrograms/dose inhaler) 50 micrograms (1 puff) twice daily

OR

» indacaterol inhaled: (75 microgram/capsule inhaler) 75 micrograms (1 capsule) once daily

OR

» arformoterol inhaled: 15 micrograms nebulized twice daily

OR

» olodaterol inhaled: (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily

OR

» tiotropium inhaled: (18 micrograms/capsule inhaler) 18 micrograms (1 capsule) once daily; (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily
### Acute

<table>
<thead>
<tr>
<th>OR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>» <strong>umeclidinium inhaled:</strong> (62.5 micrograms/dose inhaler) 62.5 micrograms (1 puff) once daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» <strong>aclidinium bromide inhaled:</strong> (400 micrograms/dose inhaler) 400 micrograms (1 puff) twice daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» <strong>glycopyrrolate inhaled:</strong> (15.6 micrograms/capsule inhaler) 15.6 micrograms (1 capsule) twice daily; (25 micrograms/vial nebulizer inhalation solution) 25 micrograms nebulized twice daily using Magnair® nebulizer device</td>
<td></td>
</tr>
</tbody>
</table>

» Long-acting muscarinic antagonists (LAMA) or long-acting beta-2 agonists (LABA)\[105\] can be used as first-line therapy in this group of patients.\[27\]

» According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, long-acting inhaled bronchodilators are superior to short-acting bronchodilators when taken as needed and are, therefore, recommended in this patient group.\[27\] \[106\] [107]

» According to GOLD guidelines, there is no evidence to recommend one class of long-acting bronchodilator over another for initial relief of symptoms in this group of patients. The choice should depend on the patient's perception of symptom relief.\[27\]

» For patients with severe breathlessness, initial therapy with two bronchodilators may be considered.\[27\]

» For patients with persistent breathlessness on monotherapy, GOLD guidelines recommend the use of two bronchodilators.\[27\]

» Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.\[102\] [103]

**plus short-acting bronchodilator as required**

Treatment recommended for ALL patients in selected patient group

**Primary options**
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>albuterol inhaled:</strong></td>
<td>(90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td><strong>levalbuterol inhaled:</strong></td>
<td>(45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td><strong>ipratropium bromide inhaled:</strong></td>
<td>(17 micrograms/dose inhaler) 34 micrograms (2 puffs) up to four times a day when required, maximum 204 micrograms/day</td>
</tr>
</tbody>
</table>

- Provides symptomatic relief.
- Failure to respond to short-acting bronchodilator may signify an acute exacerbation.
- Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[102] [103]

**plus patient education and vaccination**

Treatment recommended for ALL patients in selected patient group

- Influenza and pneumococcal vaccination should be offered to every COPD patient.[27]
  - Influenza vaccine is given annually.
  - Pneumococcal vaccine should be given to COPD patients older than 65 years of age and to younger patients with significant comorbid conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%.[104]
- Patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Physical activity is recommended for all patients with COPD.[27]
- Discussions should be held early in the course of the disease, before acute respiratory failure develops, about the possible need for and benefits of palliative care in the future.[99]

**plus smoking cessation**

Treatment recommended for ALL patients in selected patient group

- All patients should be strongly recommended not to start smoking, or to stop if they are current...
Chronic obstructive pulmonary disease (COPD)

Treatment

TREATMENT

Acute smokers. Smoking cessation is a primary goal in management of COPD.

» Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate nonpharmacologic therapies, should be used.

plus pulmonary rehabilitation

TREATMENT recommended for ALL patients in selected patient group

» Pulmonary rehabilitation should be started early.[27]

» The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. Pulmonary rehabilitation can result in significant and clinically meaningful improvements in multiple outcome areas, including dyspnea, exercise ability, health status, and healthcare utilization.[27] [91]

adjunct long-term oxygen therapy

TREATMENT recommended for SOME patients in selected patient group

» Criteria for long-term oxygen therapy include: PaO₂ ≤7.3 kPa (55 mmHg); or SaO₂ ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO₂ between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO₂ of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).[27]

» Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg).[27] These patients usually have a saturation of <92% in room air at sea level. If in doubt, patients could undergo testing to be evaluated for their predicted PaO₂ during flight.

» The therapeutic goal is to increase the PaO₂ to at least 5 mmHg above the patient’s baseline value and to a minimum of 60 mmHg. In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep.[91] [96]

2nd dual long-acting bronchodilator therapy

Primary options

» umeclidinium/vilanterol inhaled: (62.5/25 micrograms/dose inhaler) 1 puff once daily

OR
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>» glycopyrrolate/formoterol fumarate inhaled:</strong> (9/4.8 micrograms/dose inhaler) 2 puffs twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td><strong>» indacaterol/glycopyrrolate inhaled:</strong> (27.5/15.6 micrograms/capsule inhaler) 1 capsule twice daily</td>
<td></td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td><strong>» tiotropium/olodaterol inhaled:</strong> (2.5/2.5 micrograms/dose inhaler) 2 puffs once daily</td>
<td></td>
</tr>
</tbody>
</table>

**» For patients with persistent breathlessness on monotherapy, Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of two bronchodilators.**[27]

**» If two bronchodilators do not improve symptoms, GOLD guidelines suggest stepping down again to a single bronchodilator.**[27]

**» Umeclidinium/vilanterol, glycopyrrolate/formoterol fumarate,**[47] **indacaterol/glycopyrrolate,**[51] **and tiotropium/olodaterol are combinations of a long-acting beta-2 agonist (LABA) and a long-acting muscarinic antagonist (LAMA) approved for use in COPD.**[46]

### plus short-acting bronchodilator as required

**Treatment recommended for ALL patients in selected patient group**

#### Primary options

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>» albuterol inhaled:</strong> (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required</td>
<td></td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td><strong>» levalbuterol inhaled:</strong> (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required</td>
<td></td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
<tr>
<td><strong>» ipratropium bromide inhaled:</strong> (17 micrograms/dose inhaler) 34 micrograms (2 puffs) up to four times a day when required, maximum 204 micrograms/day</td>
<td></td>
</tr>
</tbody>
</table>

**» Provides symptomatic relief.**
## Chronic obstructive pulmonary disease (COPD)

### Treatment

#### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Failure to respond to short-acting bronchodilator may signify an acute exacerbation.</td>
</tr>
<tr>
<td></td>
<td>Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium. [102] [103]</td>
</tr>
</tbody>
</table>

**plus** patient education and vaccination

<table>
<thead>
<tr>
<th>Description</th>
<th>Treatment recommended for ALL patients in selected patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Influenza and pneumococcal vaccination should be offered to every COPD patient.</strong> [27]</td>
</tr>
<tr>
<td></td>
<td>Influenza vaccine is given annually. Pneumococcal vaccine should be given to COPD patients older than 65 years of age and to younger patients with significant comorbid conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of &lt;40%. [104]</td>
</tr>
<tr>
<td></td>
<td>Patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Physical activity is recommended for all patients with COPD. [27]</td>
</tr>
<tr>
<td></td>
<td>Discussions should be held early in the course of the disease, before acute respiratory failure develops, about the possible need for and benefits of palliative care in the future. [99]</td>
</tr>
</tbody>
</table>

**plus** smoking cessation

<table>
<thead>
<tr>
<th>Description</th>
<th>Treatment recommended for ALL patients in selected patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>All patients should be strongly recommended not to start smoking, or to stop if they are current smokers. Smoking cessation is a primary goal in management of COPD.</strong></td>
</tr>
<tr>
<td></td>
<td>Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate nonpharmacologic therapies, should be used.</td>
</tr>
</tbody>
</table>

**plus** pulmonary rehabilitation

<table>
<thead>
<tr>
<th>Description</th>
<th>Treatment recommended for ALL patients in selected patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Pulmonary rehabilitation should be started early.</strong> [27]</td>
</tr>
<tr>
<td></td>
<td>The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. Pulmonary rehabilitation can result in significant and clinically meaningful improvements in multiple outcome areas, including dyspnea,</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Acute

**adjunct**

**long-term oxygen therapy**

Treatment recommended for SOME patients in selected patient group

> Criteria for long-term oxygen therapy include:
> PaO₂ ≤7.3 kPa (55 mmHg); or SaO₂ ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO₂ between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO₂ of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).[27]

> Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg).[27] These patients usually have a saturation of <92% in room air at sea level. If in doubt, patients could undergo testing to be evaluated for their predicted PaO₂ during flight.

> The therapeutic goal is to increase the PaO₂ to at least 5 mmHg above the patient's baseline value and to a minimum of 60 mmHg. In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep.[91] [96]

### group C: few symptoms but higher risk of exacerbations

1st long-acting bronchodilator

**Primary options**

> **tiotropium inhaled**:
> (18 micrograms/capsule inhaler) 18 micrograms (1 capsule) once daily; (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily

OR

> **umeclidinium inhaled**:
> (62.5 micrograms/dose inhaler) 62.5 micrograms (1 puff) once daily

OR

> **aclidinium bromide inhaled**:
> (400 micrograms/dose inhaler) 400 micrograms (1 puff) twice daily

OR

> **glycopyrrolate inhaled**:
> (15.6 micrograms/capsule inhaler) 15.6 micrograms (1 capsule)
### Acute

- **Treatment**
  - twice daily; (25 micrograms/vial nebulizer inhalation solution) 25 micrograms nebulized twice daily using Magnair® nebulizer device

- **Initial treatment in group C should be a single long-acting bronchodilator.**[^27] In two head-to-head comparisons, the tested long-acting muscarinic antagonist (LAMA) was better than the long-acting beta-2 agonist (LABA) at preventing exacerbations.[^42] [^43] Therefore, Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend starting with a LAMA in patient group C.

- **Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[^102] [^103]**

### Plus short-acting bronchodilator as required

**Treatment recommended for ALL patients in selected patient group**

#### Primary options

- **albuterol inhaled:** (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required

  **OR**

- **levalbuterol inhaled:** (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required

  **OR**

- **ipratropium bromide inhaled:** (17 micrograms/dose inhaler) 34 micrograms (2 puffs) up to four times a day when required, maximum 204 micrograms/day

- **Provides symptomatic relief.**

- **Failure to respond to short-acting bronchodilator may signify an acute exacerbation.**

- **Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[^102] [^103]**

### Plus patient education and vaccination

**Treatment recommended for ALL patients in selected patient group**

- **Influenza and pneumococcal vaccination should be offered to every COPD patient.[^27]**

Influenza vaccine is given annually.
### Acute

Pneumococcal vaccine should be given to COPD patients older than 65 years of age and to younger patients with significant comorbid conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%.[104]

» Patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Physical activity is recommended for all patients with COPD.[27]

» Discussions should be held early in the course of the disease, before acute respiratory failure develops, about the possible need for and benefits of palliative care in the future.[99]

**plus** smoking cessation

Treatment recommended for ALL patients in selected patient group

» All patients should be strongly recommended not to start smoking, or to stop if they are current smokers. Smoking cessation is a primary goal in management of COPD.

» Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate nonpharmacologic therapies, should be used.

**plus** pulmonary rehabilitation

Treatment recommended for ALL patients in selected patient group

» Pulmonary rehabilitation should be started early.[27]

» The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. Pulmonary rehabilitation can result in improvements in multiple outcome areas, including dyspnea, exercise, quality of life, and emotional feelings.[27][91]

**adjunct** theophylline

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **theophylline**: 300 mg/day orally (immediate-release) initially given in divided doses every 6-8 hours, increase to 400 mg/day after 3 days, then 600 mg/day after another 3 days; adjust dose according to serum drug level and response
### Acute

» There is no clear recommendation about the exactly appropriate time to use theophylline, but most experts believe in its use when patients have exhausted bronchodilator and corticosteroid options.

» Toxicity is dose-related.

### Adjunct

**long-term oxygen therapy**

Treatment recommended for SOME patients in selected patient group

» Criteria for long-term oxygen therapy include: PaO₂ ≤7.3 kPa (55 mmHg); or SaO₂ ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO₂ between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO₂ of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%). [27]

» Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg). [27] These patients usually have a saturation of <92% in room air at sea level. If in doubt, patients could undergo testing to be evaluated for their predicted PaO₂ during flight.

» The therapeutic goal is to increase the PaO₂ to at least 5 mmHg above the patient's baseline value and to a minimum of 60 mmHg. In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep. [91] [96]

### 2nd

**dual long-acting bronchodilator therapy**

**Primary options**

» **umeclidinium/vilanterol inhaled**: (62.5/25 micrograms/dose inhaler) 1 puff once daily

OR

» **glycopyrrlate/formoterol fumarate inhaled**: (9/4.8 micrograms/dose inhaler) 2 puffs twice daily

OR

» **indacaterol/glycopyrrlate inhaled**: (27.5/15.6 micrograms/capsule inhaler) 1 capsule twice daily

OR

» **tiotropium/olodaterol inhaled**: (2.5/2.5 micrograms/dose inhaler) 2 puffs once daily
Chronic obstructive pulmonary disease (COPD)

### Treatment

#### Acute

- **Patients in group C with persistent exacerbations may benefit from dual therapy with a long-acting beta-2 agonist (LABA) and a long-acting muscarinic antagonist (LAMA).** [27]

- **Umeclidinium/vilanterol, glycopyrrolate/formoterol fumarate,** [47] **indacaterol/glycopyrrolate,** [51] **and tiotropium/olodaterol are combinations of a LABA and a LAMA approved for use in COPD.** [46]

  
  **plus short-acting bronchodilator as required**

  Treatment recommended for ALL patients in selected patient group

  **Primary options**

  - **albuterol inhaled:** (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required
  - **levalbuterol inhaled:** (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required
  - **ipratropium bromide inhaled:** (17 micrograms/dose inhaler) 34 micrograms (2 puffs) up to four times a day when required, maximum 204 micrograms/day

  **plus patient education and vaccination**

  Treatment recommended for ALL patients in selected patient group

  - **Influenza and pneumococcal vaccination should be offered to every COPD patient.** [27] Influenza vaccine is given annually. Pneumococcal vaccine should be given to COPD patients older than 65 years of age and to younger patients with significant comorbid conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%. [104]
### Acute

» Patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Physical activity is recommended for all patients with COPD.[27]

» Discussions should be held early in the course of the disease, before acute respiratory failure develops, about the possible need for and benefits of palliative care in the future.[99]

#### plus smoking cessation

Treatment recommended for ALL patients in selected patient group

» All patients should be strongly recommended not to start smoking, or to stop if they are current smokers. Smoking cessation is a primary goal in management of COPD.

» Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate nonpharmacologic therapies, should be used.

#### plus pulmonary rehabilitation

Treatment recommended for ALL patients in selected patient group

» Pulmonary rehabilitation should be started early.[27]

» The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. Pulmonary rehabilitation can result in improvements in multiple outcome areas, including dyspnea, exercise, quality of life, and emotional feelings.[27] [91]

#### adjunct theophylline

Treatment recommended for SOME patients in selected patient group

**Primary options**

» **theophylline**: 300 mg/day orally (immediate-release) initially given in divided doses every 6-8 hours, increase to 400 mg/day after 3 days, then 600 mg/day after another 3 days; adjust dose according to serum drug level and response

» There is no clear recommendation about the exactly appropriate time to use theophylline, but most experts believe in its use when patients have exhausted bronchodilator and corticosteroid options.

» Toxicity is dose-related.
### Acute

**adjunct long-term oxygen therapy**

Treatment recommended for SOME patients in selected patient group

» Criteria for long-term oxygen therapy include: PaO₂ ≤7.3 kPa (55 mmHg); or SaO₂ ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO₂ between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO₂ of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).[27]

» Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg).[27] These patients usually have a saturation of <92% in room air at sea level. If in doubt, patients could undergo testing to be evaluated for their predicted PaO₂ during flight.

» The therapeutic goal is to increase the PaO₂ to at least 5 mmHg above the patient's baseline value and to a minimum of 60 mmHg. In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep.[91] [96]

### 3rd long-acting beta-2 agonist plus inhaled corticosteroid

**Primary options**

- **fluticasone furoate/vilanterol inhaled:** (100/25 micrograms/dose inhaler) 1 puff once daily

  OR

- **fluticasone propionate/salmeterol inhaled:** (250/50 micrograms/dose inhaler) 1 puff twice daily

  OR

- **budesonide/formoterol inhaled:** (160/4.5 micrograms/dose inhaler) 2 puffs twice daily

  OR

- **mometasone/formoterol inhaled:** (100/5 micrograms/dose inhaler; 200/5 micrograms/dose inhaler) 2 puffs twice daily

  » Patients with persistent exacerbations may benefit from using a combination of a long-acting beta-2 agonist (LABA) and an inhaled corticosteroid (ICS). As inhaled corticosteroids
| Acute |  
|-------|---|
| increase the risk of developing pneumonia in some patients, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines prefer dual long-acting bronchodilator therapy over a LABA/ICS combination.[27]
<p>|   » A combination preparation of a LABA and an ICS may be used for patients who require both these agents. This is convenient and may help with compliance in some patients. The choice of therapy in this class is based on availability and individual response and preference. Combination therapy with a LABA and an ICS is superior to use of either agent alone. The combination may be provided in separate inhalers or a combination inhaler (combination formulations are detailed here). |
|   plus short-acting bronchodilator as required |
| Treatment recommended for ALL patients in selected patient group |
| Primary options |
|   » albuterol inhaled: (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required |
| OR |
|   » levalbuterol inhaled: (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required |
| OR |
|   » ipratropium bromide inhaled: (17 micrograms/dose inhaler) 34 micrograms (2 puffs) up to four times a day when required, maximum 204 micrograms/day |
|   » Provides symptomatic relief. |
|   » Failure to respond to short-acting bronchodilator may signify an acute exacerbation. |
|   » Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[102] [103] |
|   plus patient education and vaccination |
| Treatment recommended for ALL patients in selected patient group |
|   » Influenza and pneumococcal vaccination should be offered to every COPD patient.[27] |
| Influenza vaccine is given annually. |</p>
<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pneumococcal vaccine should be given to COPD patients older than</td>
</tr>
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<td>65 years of age and to younger patients with significant comorbid</td>
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<td>conditions. This vaccine also reduces incidence of community-</td>
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<td>acquired pneumonia in patients younger than 65 with an FEV1 of</td>
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<td>&lt;40%. [104]</td>
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<td>recommended for all patients with COPD. [27]</td>
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<td>» Discussions should be held early in the course of the disease,</td>
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<tr>
<td></td>
<td>before acute respiratory failure develops, about the possible</td>
</tr>
<tr>
<td></td>
<td>need for and benefits of palliative care in the future. [99]</td>
</tr>
</tbody>
</table>

plus smoking cessation

| Treatment recommended for ALL patients in |                                                                 |
| selected patient group                   |                                                                 |
| » All patients should be strongly        | recommended not to start smoking, or to stop if they are current |
| smokers. Smoking cessation is a primary  | goal in management of COPD.                                      |
| goal in management of COPD.              |                                                                 |
| » Nicotine-replacement therapy or other  | drug therapies, in conjunction with appropriate nonpharmacologic |
| therapies, in conjunction with appropriate | therapies, should be used.                                      |

plus pulmonary rehabilitation

| Treatment recommended for ALL patients in |                                                                 |
| selected patient group                   |                                                                 |
| » Pulmonary rehabilitation should be     | started early. [27]                                             |
| started early. [27]                       |                                                                 |
| » The principal goals of pulmonary       | rehabilitation are to reduce symptoms, improve quality of life,  |
| rehabilitation are to reduce symptoms,   | and increase physical and emotional participation in everyday    |
| improve quality of life, and increase    | activities. Pulmonary rehabilitation can result in improvements  |
| physical and emotional participation in   | in multiple outcome areas, including dyspnea, exercise capacity,  |
| everyday activities. Pulmonary            | quality of life, and emotional feelings. [27] [91]              |
| rehabilitation can result in improvements |                                                                 |
| in multiple outcome areas, including      |                                                                 |
| dyspnea, exercise capacity, quality of    |                                                                 |
| life, and emotional feelings. [27] [91]   |                                                                 |

adjunct theophylline

| Treatment recommended for SOME patients in |                                                                 |
| selected patient group                     |                                                                 |

Primary options

- theophylline: 300 mg/day orally (immediate-release) initially given in divided doses every 6-8 hours, increase to 400 mg/day after 3 days, then 600 mg/day after another 3 days; adjust dose according to serum drug level and response
**TREATMENT**

### Acute

- There is no clear recommendation about the exactly appropriate time to use theophylline, but most experts believe in its use when patients have exhausted bronchodilator and corticosteroid options.

- Toxicity is dose-related.

### Adjunct

**long-term oxygen therapy**

Treatment recommended for SOME patients in selected patient group

- Criteria for long-term oxygen therapy include: PaO₂ ≤7.3 kPa (55 mmHg); or SaO₂ ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO₂ between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO₂ of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).[27]

- Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg).[27] These patients usually have a saturation of <92% in room air at sea level. If in doubt, patients could undergo testing to be evaluated for their predicted PaO₂ during flight.

- The therapeutic goal is to increase the PaO₂ to at least 5 mmHg above the patient’s baseline value and to a minimum of 60 mmHg. In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep.[91] [96]

### Group D: more symptoms and high risk of exacerbations

1st **dual long-acting bronchodilator therapy**

**Primary options**

- **umeclidinium/vilanterol inhaled:** (62.5/25 micrograms/dose inhaler) 1 puff once daily

  OR

- **glycopyrrolate/formoterol fumarate inhaled:** (9/4.8 micrograms/dose inhaler) 2 puffs twice daily

  OR

- **indacaterol/glycopyrrolate inhaled:** (27.5/15.6 micrograms/capsule inhaler) 1 capsule twice daily

  OR
Treatment

**Acute**

- tiotropium/olodaterol inhaled: (2.5/2.5 micrograms/dose inhaler) 2 puffs once daily

- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend starting treatment with a long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) combination in group D. This is because the LABA/LAMA combinations showed superior results compared to the single drugs in studies with patient reported outcomes as the primary endpoint.[27]

- In addition, a LABA/LAMA combination was superior to a LABA and an inhaled corticosteroid (ICS) combination in preventing exacerbations and other patient reported outcomes in group D patients.[27]

- Group D patients are at a higher risk of developing pneumonia when receiving treatment with ICS.[42] [108]

- If a single bronchodilator is chosen as initial treatment, a LAMA is preferred by GOLD guidelines over a LABA.[27]

- In some patients, initial treatment with LABA/ICS combination may be the first choice. These patients may have a history and/or findings suggestive of asthma-COPD overlap.[27]

- Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[102] [103]

- Umeclidinium/vilanterol, glycopyrrolate/formoterol fumarate,[47] indacaterol/glycopyrrolate,[51] and tiotropium/olodaterol are combinations of a LABA and a LAMA approved for use in COPD.[46]

**TREATMENT**

- **plus short-acting bronchodilator as required**

  Treatment recommended for ALL patients in selected patient group

**Primary options**

- albuterol inhaled: (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required

  **OR**

- levalbuterol inhaled: (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required
TREATMENT

Acute

OR

- ipratropium bromide inhaled: (17 micrograms/dose inhaler) 34 micrograms (2 puffs) up to four times a day when required, maximum 204 micrograms/day

  » Provides symptomatic relief.
  
  » Failure to respond to short-acting bronchodilator may signify an acute exacerbation.
  
  » Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.\[102\] \[103\]

plus patient education and vaccination

Treatment recommended for ALL patients in selected patient group

- Influenza and pneumococcal vaccination should be offered to every COPD patient.\[27\]
  Influenza vaccine is given annually. Pneumococcal vaccine should be given to COPD patients older than 65 years of age and to younger patients with significant comorbid conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%.\[104\]

  » Patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Physical activity is recommended for all patients with COPD.\[27\]

plus smoking cessation

Treatment recommended for ALL patients in selected patient group

- All patients should be strongly recommended not to start smoking, or to stop if they are current smokers. Smoking cessation is a primary goal in management of COPD.

  » Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate nonpharmacologic therapies, should be used.

plus pulmonary rehabilitation

Treatment recommended for ALL patients in selected patient group

- Pulmonary rehabilitation should be started as early as patient group B or C disease.\[27\]

  » The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional
## Chronic obstructive pulmonary disease (COPD)

### Acute participation

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease that affects the flow of air in and out of the lungs. Pulmonary rehabilitation can result in improvements in multiple outcome areas, including dyspnea, exercise capacity, quality of life, and emotional feelings.[27] [91]

### Adjunct theophylline

Treatment recommended for SOME patients in selected patient group

#### Primary options

- **theophylline**: 300 mg/day orally (immediate-release) initially given in divided doses every 6-8 hours, increase to 400 mg/day after 3 days, then 600 mg/day after another 3 days; adjust dose according to serum drug level and response

  - There is no clear recommendation about the exactly appropriate time to use theophylline, but most experts believe in its use when patients have exhausted bronchodilator and corticosteroid options.

  - Toxicity is dose-related.

### Adjunct long-term oxygen therapy

Treatment recommended for SOME patients in selected patient group

- Criteria for long-term oxygen therapy include: PaO₂ ≤7.3 kPa (55 mmHg); or SaO₂ ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO₂ between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO₂ of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).[27]

  - Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg).[27] These patients usually have a saturation of <92% in room air at sea level. If in doubt, patients could undergo testing to be evaluated for their predicted PaO₂ during flight.

  - The therapeutic goal is to increase the PaO₂ to at least 5 mmHg above the patient's baseline value and to a minimum of 60 mmHg. In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep.[91] [96]

### Adjunct surgical interventions

Treatment recommended for SOME patients in selected patient group
Criteria for referral for lung transplantation include: progressive disease, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy; patient is not a candidate for endoscopic or surgical lung volume reduction surgery (LVRS) (simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate); Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index of 5 to 6; PaCO₂ >50 mmHg or 6.6 kPa and/or PaO₂ <60 mmHg or 8 kPa; FEV1 <25% predicted.

LVRS is indicated in patients with very severe airflow limitation and especially in patients with localized upper lobe disease and lower than normal exercise capacity. Bullectomy is an option in COPD patients with dyspnea in whom CT reveals huge bullae occupying at least 30% of the hemithorax. Severely poor functional status and severe decrease in FEV1 (<500 mL) make these options less favorable.

Lung transplantation has been shown to improve quality of life and functional capacity. However, lung transplantation does not appear to confer a survival benefit.

adjunct palliative care

For some patients with very advanced end-stage COPD, palliative care and hospice admission should be considered. Patient and family should be well educated about the process, and it is suggested that discussions should be held early in the course of the disease before acute respiratory failure develops. One study has suggested that low doses of an opioid analgesic and a benzodiazepine are safe and are not associated with increased hospital admissions or mortality. One Cochrane review concluded that there is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD.

2nd triple therapy: long-acting beta-2 agonist (LABA) plus long-acting muscarinic antagonist (LAMA) plus inhaled corticosteroid (ICS)

Primary options
### Chronic obstructive pulmonary disease (COPD)

#### Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>» fluticasone furoate/umeclidinium/vilanterol inhaled: (100/62.5/25 micrograms/dose inhaler) 1 puff once daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» fluticasone furoate/vilanterol inhaled: (100/25 micrograms/dose inhaler) 1 puff once daily</td>
<td></td>
</tr>
<tr>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» fluticasone propionate/salmeterol inhaled: (250/50 micrograms/dose inhaler) 1 puff twice daily</td>
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<tr>
<td>-or-</td>
<td></td>
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<tr>
<td>» budesonide/formoterol inhaled: (160/4.5 micrograms/dose inhaler) 2 puffs twice daily</td>
<td></td>
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<tr>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» mometasone/formoterol inhaled: (100/5 micrograms/dose inhaler; 200/5 micrograms/dose inhaler) 2 puffs twice daily</td>
<td></td>
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<tr>
<td>--AND--</td>
<td></td>
</tr>
<tr>
<td>» tiotropium inhaled: (18 micrograms/capsule inhaler) 18 micrograms (1 capsule) once daily; (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily</td>
<td></td>
</tr>
<tr>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» umeclidinium inhaled: (62.5 micrograms/dose inhaler) 62.5 micrograms (1 puff) once daily</td>
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</tr>
<tr>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» aclidinium bromide inhaled: (400 micrograms/dose inhaler) 400 micrograms (1 puff) twice daily</td>
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</tr>
<tr>
<td>-or-</td>
<td></td>
</tr>
<tr>
<td>» glycopyrrolate inhaled: (15.6 micrograms/capsule inhaler) 15.6 micrograms (1 capsule) twice daily; (25 micrograms/vial nebulizer inhalation solution) 25 micrograms nebulized twice daily using Magnair® nebulizer device</td>
<td></td>
</tr>
</tbody>
</table>

» In group D patients who develop further exacerbations on LABA/LAMA therapy, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest two alternative pathways: escalation to LABA/LAMA/ICS or switch to LABA/ICS.[27]

» Multiple studies support triple therapy with LABA/LAMA/ICS as being superior to single- or double-agent therapy with LABA/LAMA or LABA/ICS regarding rate of moderate to severe COPD exacerbations[65] [66] [67] [68] and rate of hospitalization.[69] [70]

» If patients treated with LABA/LAMA/ICS (triple therapy) still have exacerbations, additional options include adding roflumilast, adding a...
### Acute

macrolide antibiotic, and stopping the ICS.[27]

Stopping the ICS may be appropriate if a lack of efficacy is reported, if there is an elevated risk of adverse events (including pneumonia), or if there would be no significant harm from withdrawal of ICS.[27]

**plus** short-acting bronchodilator as required

Treatment recommended for ALL patients in selected patient group

**Primary options**

**»** albuterol inhaled: (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required

OR

**»** levalbuterol inhaled: (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required

OR

**»** ipratropium bromide inhaled: (17 micrograms/dose inhaler) 34 micrograms (2 puffs) up to four times a day when required, maximum 204 micrograms/day

**»** Provides symptomatic relief.

**»** Failure to respond to short-acting bronchodilator may signify an acute exacerbation.

**»** Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[102] [103]

**plus** patient education and vaccination

Treatment recommended for ALL patients in selected patient group

**»** Influenza and pneumococcal vaccination should be offered to every COPD patient.[27]

Influenza vaccine is given annually.

Pneumococcal vaccine should be given to COPD patients older than 65 years of age and to younger patients with significant comorbid conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%.[104]

**»** Patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Physical activity is recommended for all patients with COPD.[27]
### Chronic obstructive pulmonary disease (COPD)  
### Treatment

#### Acute

<table>
<thead>
<tr>
<th>plus</th>
<th>smoking cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td>» All patients should be strongly recommended not to start smoking, or to stop if they are current smokers. Smoking cessation is a primary goal in management of COPD.</td>
<td></td>
</tr>
<tr>
<td>» Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate nonpharmacologic therapies, should be used.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>plus</th>
<th>pulmonary rehabilitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td>» Pulmonary rehabilitation should be started as early as patient group B or C disease.[27]</td>
<td></td>
</tr>
<tr>
<td>» The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. Pulmonary rehabilitation can result in improvements in multiple outcome areas, including dyspnea, exercise capacity, quality of life, and emotional feelings.[27] [91]</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>adjunct</th>
<th>theophylline</th>
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</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

#### Primary options

- **theophylline**: 300 mg/day orally (immediate-release) initially given in divided doses every 6-8 hours, increase to 400 mg/day after 3 days, then 600 mg/day after another 3 days; adjust dose according to serum drug level and response

- There is no clear recommendation about the exactly appropriate time to use theophylline, but most experts believe in its use when patients have exhausted bronchodilator and corticosteroid options.

- Toxicity is dose-related.

<table>
<thead>
<tr>
<th>adjunct</th>
<th>phosphodiesterase-4 inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

#### Primary options

- **roflumilast**: 500 micrograms orally once daily
### Acute

- **Roflumilast** may be considered in patients with an FEV1 <50% predicted and chronic bronchitis,[112] especially if they have experienced at least one hospitalization for an exacerbation in the previous year.[27] [113]

<table>
<thead>
<tr>
<th><strong>adjunct</strong></th>
<th><strong>macrolide antibiotic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for some patients in selected patient group</td>
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</tr>
</tbody>
</table>

**Primary options**

- **azithromycin**: 250 mg orally once daily; or 500 mg orally three times weekly

**OR**

- **erythromycin base**: 500 mg orally twice daily

- The use of azithromycin is supported by the best available evidence.[114] [115]

- Decision making should take into account the potential development of resistant organisms.

<table>
<thead>
<tr>
<th><strong>adjunct</strong></th>
<th><strong>long-term oxygen therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for some patients in selected patient group</td>
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</tbody>
</table>

- Criteria for long-term oxygen therapy include: PaO$_2$ ≤7.3 kPa (55 mmHg); or SaO$_2$ ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO$_2$ between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO$_2$ of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).[27]

- Oxygen is suggested for patients in whom the predicted PaO$_2$ during air travel is <6.7 kPa (<50 mmHg).[27] These patients usually have a saturation of <92% in room air at sea level. If in doubt, patients could undergo testing to be evaluated for their predicted PaO$_2$ during flight.

- The therapeutic goal is to increase the PaO$_2$ to at least 5 mmHg above the patient’s baseline value and to a minimum of 60 mmHg. In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep.[91] [96]

<table>
<thead>
<tr>
<th><strong>adjunct</strong></th>
<th><strong>surgical interventions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for some patients in selected patient group</td>
<td></td>
</tr>
</tbody>
</table>

- Criteria for referral for lung transplantation include: progressive disease, despite maximal
### Chronic obstructive pulmonary disease (COPD)

**Treatment**

#### Acute

<table>
<thead>
<tr>
<th>Adjunct procedures</th>
<th>treatment including medication, pulmonary rehabilitation, and oxygen therapy; patient is not a candidate for endoscopic or surgical lung volume reduction surgery (LVRS) (simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate); Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index of 5 to 6; PaCO₂ &gt;50 mmHg or 6.6 kPa and/or PaO₂ &lt;60 mmHg or 8 kPa; FEV1 &lt;25% predicted.[98]</th>
</tr>
</thead>
</table>

» LVRS is indicated in patients with very severe airflow limitation and especially in patients with localized upper lobe disease and lower than normal exercise capacity.[94] Bullectomy is an option in COPD patients with dyspnea in whom CT reveals huge bullae occupying at least 30% of the hemithorax. Severely poor functional status and severe decrease in FEV1 (<500 mL) make these options less favorable.

» Lung transplantation has been shown to improve quality of life and functional capacity.[109] [110] However, lung transplantation does not appear to confer a survival benefit.[111]

#### Palliative care

<table>
<thead>
<tr>
<th>Adjunct palliative care</th>
<th>Treatment recommended for SOME patients in selected patient group</th>
</tr>
</thead>
</table>

» For some patients with very advanced end-stage COPD, palliative care and hospice admission should be considered. Patient and family should be well educated about the process, and it is suggested that discussions should be held early in the course of the disease before acute respiratory failure develops.[99]

One study has suggested that low doses of an opioid analgesic and a benzodiazepine are safe and are not associated with increased hospital admissions or mortality.[100] One Cochrane review concluded that there is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD.[101]

#### Long-acting beta-2 agonist (LABA) plus inhaled corticosteroid (ICS)

**Primary options**

| Fluticasone furoate/vilanterol inhaled: (100/25 micrograms/dose inhaler) 1 puff once daily |

**OR**
Chronic obstructive pulmonary disease (COPD)

**Acute**

- **fluticasone propionate/salmeterol inhaled:** (250/50 micrograms/dose inhaler) 1 puff twice daily

  OR

- **budesonide/formoterol inhaled:** (160/4.5 micrograms/dose inhaler) 2 puffs twice daily

  OR

- **mometasone/formoterol inhaled:** (100/5 micrograms/dose inhaler; 200/5 micrograms/dose inhaler) 2 puffs twice daily

  In group D patients who develop further exacerbations while taking a combination of a LABA and a long-acting muscarinic antagonist (LAMA), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest two alternative pathways: escalation to LABA/LAMA/ICS or switch to LABA/ICS.[27]

  - There is no evidence that switching from LABA/LAMA to LABA/ICS results in better prevention of exacerbations. If LABA/ICS therapy does not positively impact exacerbations or symptoms, a LAMA can be added.[27]

  - In some patients, initial treatment with LABA/ICS may be the first choice. These patients may have a history and/or findings suggestive of asthma-COPD overlap.[27]

  **plus short-acting bronchodilator as required**

  Treatment recommended for ALL patients in selected patient group

**Primary options**

- **albuterol inhaled:** (90 micrograms/dose inhaler) 90-180 micrograms (1-2 puffs) every 4-6 hours when required

  OR

- **levalbuterol inhaled:** (45 micrograms/dose inhaler) 45-90 micrograms (1-2 puffs) every 4-6 hours when required

  OR

- **ipratropium bromide inhaled:** (17 micrograms/dose inhaler) 34 micrograms (2
**Acute**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Action</th>
</tr>
</thead>
</table>
| Acute | **puffs** up to four times a day when required, maximum 204 micrograms/day

- Provides symptomatic relief.
- Failure to respond to short-acting bronchodilator may signify an acute exacerbation.
- Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[102] [103]

**plus** **patient education and vaccination**

Treatment recommended for ALL patients in selected patient group

- Influenza and pneumococcal vaccination should be offered to every COPD patient.[27] Influenza vaccine is given annually. Pneumococcal vaccine should be given to COPD patients older than 65 years of age and to younger patients with significant comorbid conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%. [104]

- Patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Physical activity is recommended for all patients with COPD.[27]

**plus** **smoking cessation**

Treatment recommended for ALL patients in selected patient group

- All patients should be strongly recommended not to start smoking, or to stop if they are current smokers. Smoking cessation is a primary goal in management of COPD.

- Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate nonpharmacologic therapies, should be used.

**plus** **pulmonary rehabilitation**

Treatment recommended for ALL patients in selected patient group

- Pulmonary rehabilitation should be started as early as patient group B or C disease.[27]

- The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. Pulmonary rehabilitation can result in improvements in multiple outcome areas, including dyspnea,
TREATMENT

Chronic obstructive pulmonary disease (COPD)

Acute

exercise capacity, quality of life, and emotional feelings.\[27\] [91]

adjunct theophylline

Treatment recommended for SOME patients in selected patient group

Primary options

- theophylline: 300 mg/day orally (immediate-release) initially given in divided doses every 6-8 hours, increase to 400 mg/day after 3 days, then 600 mg/day after another 3 days; adjust dose according to serum drug level and response

- There is no clear recommendation about the exactly appropriate time to use theophylline, but most experts believe in its use when patients have exhausted bronchodilator and corticosteroid options.

- Toxicity is dose-related.

adjunct long-term oxygen therapy

Treatment recommended for SOME patients in selected patient group

- Criteria for long-term oxygen therapy include: PaO\(_2\) ≤7.3 kPa (55 mmHg); or SaO\(_2\) ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO\(_2\) between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO\(_2\) of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).\[27\]

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- The therapeutic goal is to increase the PaO\(_2\) to at least 5 mmHg above the patient’s baseline value and to a minimum of 60 mmHg. In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep.\[91\] [96]

adjunct surgical interventions

Treatment recommended for SOME patients in selected patient group

- Criteria for referral for lung transplantation include: progressive disease, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy; patient is...
Chronic obstructive pulmonary disease (COPD)  Treatment

Acute

not a candidate for endoscopic or surgical lung volume reduction surgery (LVRS) (simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate); Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index of 5 to 6; PaCO₂ >50 mmHg or 6.6 kPa and/or PaO₂ <60 mmHg or 8 kPa; FEV₁ <25% predicted.[98]

» LVRS is indicated in patients with very severe airflow limitation and especially in patients with localized upper lobe disease and lower than normal exercise capacity.[94] Bullectomy is an option in COPD patients with dyspnea in whom CT reveals huge bullae occupying at least 30% of the hemithorax. Severely poor functional status and severe decrease in FEV₁ (<500 mL) make these options less favorable.

» Lung transplantation has been shown to improve quality of life and functional capacity.[109] [110] However, lung transplantation does not appear to confer a survival benefit.[111]

adjunct palliative care

Treatment recommended for SOME patients in selected patient group

» For some patients with very advanced end-stage COPD, palliative care and hospice admission should be considered. Patient and family should be well educated about the process, and it is suggested that discussions should be held early in the course of the disease before acute respiratory failure develops.[99] One study has suggested that low doses of an opioid analgesic and a benzodiazepine are safe and are not associated with increased hospital admissions or mortality.[100] One Cochrane review concluded that there is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD.[101]
Emerging Medical therapies

The increasing awareness of the role of inflammation in COPD has led to consideration of drugs that attack various targets in the inflammatory cascade. Many broad-spectrum anti-inflammatory drugs are now in phase 3 development for COPD and may enter the COPD market within the next decade. Nitric oxide inhibitors, leukotriene modifiers, and tumor necrosis factor antagonists are among these novel therapies.\[116\] Long-term (≥6 months) treatment with acetylcysteine may decrease exacerbation prevalence but does not appear to affect exacerbation rate, lung volumes, or FEV1.\[117\] Antiplatelet therapy is associated with decreased all-cause mortality in patients with COPD, independent of cardiovascular risk.\[118\] Epidermal growth factor receptor kinase has potential to combat mucus overproduction. Therapy to inhibit fibrosis is being developed. There is also a search for serine protease and matrix metalloproteinase inhibitors to prevent lung destruction and the subsequent development of emphysema, as well as drugs such as retinoid that may even reverse this process.\[119\] HMG-CoA reductase inhibitors are emerging medications in COPD that have been shown to improve some outcomes, with some improvement in lung function of COPD patients with moderate to severe class.\[120\] Although retrospective studies showed decreased rate and severity of exacerbations, hospitalization, and mortality in patients using statin therapy, especially in patients with coexisting cardiovascular disease (CVD) or hyperlipidemia, a prospective study failed to prove this benefit.\[121\] In a meta-analysis of randomized controlled trials of patients with COPD taking statins, clinical outcomes were better in patients with coexisting CVD, elevated baseline C-reactive protein, or a high cholesterol level.\[122\] Efficacy and safety of synthetic ghrelin hormone therapy in COPD patients with severely decreased physical performance and cachexia is under investigation with some promising initial results.\[123\] Palovarotene is a selective retinoic acid receptor gamma agonist that is under investigation for the treatment of emphysema. It is hypothesized that retinoic acid signaling affects alveologenesis. There have been promising results in animal studies.\[124\] Many combinations of inhaler therapies are being introduced for COPD treatment. Aclidinium/formoterol is a long-acting muscarinic antagonist and long-acting beta-2 agonist (LABA/LAMA) combination therapy that is available in some countries, but is awaiting approval by the Food and Drug Administration (FDA) in the US.

Interventional therapies

Target lobe volume reduction, a novel technique for selective bronchoscopic lung volume resection, has now become available. In this technique, a one-way valve is inserted into the hyperinflated and emphysematous segment, leading to the collapse of the nonfunctional lung segment. Promising reports have been released from case series of patients undergoing this therapy. This approach is an alternative to surgical lung volume reduction in COPD patients who are likely to require surgery.\[125\] [126]

Pharmacogenomic therapy

Pharmacogenomic therapy may be important in COPD. It is important to identify the genetic factors that determine why certain heavy smokers develop COPD and others do not. Identification of genes that predispose to the development of COPD may provide novel therapeutic targets.\[127\] [128]

Club cell protein 16 augmentation

Club cell protein 16 (CC16) is mainly produced by the Club cells (formerly known as Clara cells) in the respiratory tract epithelium. CC16 has anti-inflammatory properties in smoke-exposed lungs, and COPD is associated with CC16 deficiency. Experimental augmentation of CC16 levels reduces inflammation and cellular injury, and so CC16 augmentation may be a new disease-modifying treatment for COPD.\[129\]
**Recommendations**

**Monitoring**

Patients with COPD should be evaluated on a regular basis depending on the severity of disease. Mild stable COPD patients may be followed up at 6-month intervals, while patients with severe, frequent exacerbations and recently hospitalized patients need follow-up at 2-week to 1-month intervals. In follow-up sessions, patients should be evaluated to determine adherence to medical regimen, response to therapy, and disease progression. The level of dyspnea at rest and with exercise should be determined, as well as number of exacerbations. Questionnaires such as the COPD Assessment Test (CAT) can be used to assess symptoms. These can be found in the GOLD guidelines.[1] Smoking status and smoke exposure should be determined at each appointment, followed by appropriate action.[1]

PFTs should be monitored at least every 3 years, to evaluate response to therapy and possible need for change in medications. If any significant change in medication is made or if the patient is on systemic corticosteroids, more frequent PFT monitoring is required. The GOLD guidelines recommend measuring FEV₁ by spirometry at least once a year to identify patients who are declining quickly.[1] Oxygen saturation should be monitored and patients evaluated periodically for the need of supplemental oxygen. Patients need to be monitored for short-term and long-term complications of COPD. Patient weight, nutrition status, and physical activity should also be monitored. Cachexia and reduced physical performance are indicators of a poor prognosis.

**Patient instructions**

All patients should be well educated about the disease course and symptoms of exacerbation or decompensation. Their expectation of the disease, treatment, and prognosis should be realistic. It is important to remember that no medicine has been shown to modify the long-term decline in lung function, and the primary goal of pharmacotherapy is to control symptoms and prevent complications.

One Cochrane review found that self-management interventions that include an action plan for acute exacerbations of COPD are associated with improvements in health-related quality of life and fewer admissions to hospital for respiratory problems. An exploratory analysis found a small, but significantly higher, respiratory-related mortality rate for self-management compared to usual care, although no excess risk of all-cause mortality was seen.[71]

One randomised controlled trial found that a telephone health coaching intervention to promote behaviour change in patients with mild COPD in primary care led to improvements in self-management activities, but did not improve health-related quality of life.[72]

Patients should stay as healthy and active as possible. It is necessary to stop active or passive smoking and avoid environmental exposure to toxic fumes.

Regular medical follow-up is necessary to optimize the treatment. If there is any worsening of symptoms, immediate medical attention is required. Patients on continuous oxygen therapy may need increase in oxygen flow during air travel.

Physical activity is recommended for all patients with COPD and they should be encouraged to maintain it.[1] One systematic review and meta-analysis of randomised controlled trials found that exercise training on its own can improve physical activity in COPD, and greater improvements can be made with the addition of physical activity counseling.[90] Another systematic review and meta-analysis found that a combination of aerobic exercise and strength training was more effective than strength training or endurance training alone in increasing the 6-minute walking distance.[91]
### Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>cor pulmonale</td>
<td>long term</td>
<td>high</td>
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<tr>
<td>Complications</td>
<td>Timeframe</td>
<td>Likelihood</td>
</tr>
<tr>
<td>cor pulmonale</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>Cor pulmonale is right-sided heart failure secondary to longstanding COPD. It is caused by chronic hypoxia and subsequent vasoconstriction in pulmonary vasculature that causes pulmonary hypertension and right-sided heart failure.</td>
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<tr>
<td>Engorged neck veins, a loud P2, lower-extremity edema, and hepatomegaly are signs of cor pulmonale.</td>
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<tr>
<td>Continuous oxygen therapy is the mainstay of therapy. Judicious use of diuretics is warranted.</td>
<td>[144]</td>
<td></td>
</tr>
<tr>
<td>recurrent pneumonia</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>Recurrent pneumonia is a common complication of COPD and a frequent cause of COPD exacerbation. Either viral or bacterial infections can be the cause.</td>
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<tr>
<td>Chronic lung and airway damage, inflammation, compromised ciliary function, and bacterial colonization are likely causes of increased vulnerability to infections. Use of long-term inhaled corticosteroids is also associated with increased risk of pneumonia in patients with COPD.</td>
<td>[141] [142]</td>
<td></td>
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<tr>
<td>Use of antibiotic therapy has shown some benefit.</td>
<td>[143] Usual treatment time is around 7 to 14 days.</td>
<td>Appropriate coverage for <em>Haemophilus influenzae</em> and <em>Streptococcus pneumoniae</em> is mandatory. Pneumococcal vaccination is strongly recommended in COPD patients.</td>
</tr>
<tr>
<td>depression</td>
<td>variable</td>
<td>high</td>
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<tr>
<td>Depression is a common consequence of COPD. If any mood change occurs, a psychiatric evaluation may be necessary.</td>
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<td></td>
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<tr>
<td>pneumothorax</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Occurs because of lung parenchyma damage with subpleural bulla formation and rupture. Spontaneous pneumothorax is very common with chronic severe cough or chest trauma, and may be life-threatening.</td>
<td></td>
<td></td>
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<tr>
<td>High levels of suspicion are necessary for prompt diagnosis. CXR or chest CT confirms the diagnosis.</td>
<td>[Fig-4]</td>
<td></td>
</tr>
<tr>
<td>Conservative management may be sufficient in minor cases. In severe cases, chest tube insertion is necessary to prevent tension pneumothorax and hemodynamic instability. If recurrent pneumothorax occurs, then surgical interventions, such as video-assisted thoracoscopy pleurodesis or bullectomy, are warranted.</td>
<td></td>
<td></td>
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<tr>
<td>respiratory failure</td>
<td>variable</td>
<td>medium</td>
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<tr>
<td>A study of a large number of COPD patients with acute respiratory failure reported inhospital mortality of 17% to 49%.</td>
<td>[140] Therapy includes noninvasive positive pressure ventilation and/or mechanical ventilation.</td>
<td></td>
</tr>
<tr>
<td>anemia</td>
<td>variable</td>
<td>medium</td>
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</tbody>
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60
Chronic obstructive pulmonary disease (COPD)

<table>
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<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>Anemia is more prevalent than previously thought, affecting almost 25% of COPD patients. A low hematocrit indicates a poor prognosis in COPD patients receiving long-term oxygen treatment.</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>polycythemia</td>
<td>variable</td>
<td>medium</td>
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<tr>
<td>Secondary polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers. It can be identified by hematocrit &gt;55%. Many times these patients require supplemental home oxygen.</td>
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### Prognosis

COPD is a disease with an indeterminate course and variable prognosis. Its prognosis depends on several factors including genetic predisposition, environmental exposures, comorbidities and, to a lesser degree, acute exacerbations.

Although short-term survival for patients with COPD and respiratory failure depends on the overall severity of acute illness, long-term survival is primarily influenced by the severity of COPD and the presence of comorbid conditions. Traditionally, prognosis has been reported based on the FEV1, which is a part of pulmonary function testing. A meta-regression analysis showed a significant correlation between increased FEV1 and lower risk of COPD exacerbation. In addition to the FEV1, other factors that predict prognosis are weight (very low weight is a negative prognostic factor), distance walked in 6 minutes, and degree of shortness of breath with activities. These factors, known as the Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index, can be used to provide information on prognosis for 1-year, 2-year, and 4-year survival. One study revealed that plasma pro-adrenomedullin concentration plus BODE index is a better prognostic tool than BODE index alone. Elevation of adrenomedullin, arginine vasopressin, atrial natriuretic peptide, and C-reactive protein is associated with increased risk of death in patients with stable COPD. Recently, more interest has been put on comorbidities and prior exacerbations as the predictor of COPD course. CODEX index (comorbidities, obstruction, dyspnea, and previous severe exacerbations) is proved to be superior to BODE index in predicting prognosis for COPD patients. Frequent COPD exacerbations and requirement for multiple intubation and invasive mechanical ventilation for acute respiratory failure in COPD patients are markers of poor prognosis.

Among different therapeutic modalities in COPD, the only two factors that improve survival are smoking cessation and oxygen supplementation.
### Diagnostic guidelines

**International**

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<tr>
<th>Guideline</th>
<th>Published by</th>
<th>Last published</th>
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<tr>
<td>Global strategy for the diagnosis, management, and prevention of COPD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
<td>2019</td>
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<td>(<a href="https://goldcopd.org/gold-reports/">https://goldcopd.org/gold-reports/</a>) [26]</td>
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<td></td>
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<tr>
<td>Enhancing implementation, use, and delivery of pulmonary rehabilitation</td>
<td>American Thoracic Society; European Respiratory Society</td>
<td>2015</td>
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<td>(<a href="https://www.thoracic.org/statements/pulmonary-rehab.php">https://www.thoracic.org/statements/pulmonary-rehab.php</a>) [130]</td>
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<td>BTS/ICS guidelines for the ventilatory management of acute hypercapnic</td>
<td>British Thoracic Society; Intensive Care Society</td>
<td>2017</td>
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<td>respiratory failure in adults</td>
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<td>(<a href="https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btsics-gui">https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btsics-gui</a></td>
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<td>delines-for-the-ventilatory-management-of-acute-hypercapnic-respirator</td>
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<td>i-failure-in-adults/) [131]</td>
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<td>Nursing care of dyspnea: the 6th vital sign in individuals with chronic</td>
<td>Registered Nurses Association of Ontario</td>
<td>2010</td>
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<td>obstructive pulmonary disease (COPD)</td>
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</tbody>
</table>
Key articles


References


Chronic obstructive pulmonary disease (COPD)

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52. Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD.


Figure 1: COPD chest x-ray (AP view): hyperinflated lung, flattened diaphragm, increased intercostal spaces

From the collection of Manoochehr Abadian Sharifabad, MD
Figure 2: COPD chest x-ray (lateral view): hyperinflated lung, flattened diaphragm, increased antero-posterior diameter (barrel chest) in lateral view

From the collection of Manoochehr Abadian Sharifabad, MD
Figure 3: COPD chest CT: hyperinflated lung, emphysematous changes, and increased antero-posterior diameter (barrel chest)

From the collection of Manoochehr Abadian Sharifabad, MD
**Figure 4: Chest CT: severe COPD changes with right pneumothorax**

*From the collection of Manoochehr Abadian Sharifabad, MD*
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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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