COPD

The right clinical information, right where it's needed
# Table of Contents

## Summary

## Basics
- Definition 4
- Epidemiology 4
- Aetiology 4
- Pathophysiology 4

## Prevention
- Primary prevention 6
- Screening 6
- Secondary prevention 6

## Diagnosis
- Case history 7
- Step-by-step diagnostic approach 7
- Risk factors 9
- History & examination factors 10
- Diagnostic tests 12
- Differential diagnosis 14
- Diagnostic criteria 15

## Treatment
- Step-by-step treatment approach 17
- Treatment details overview 22
- Treatment options 26
- Emerging 60

## Follow up
- Recommendations 61
- Complications 61
- Prognosis 63

## Guidelines
- Diagnostic guidelines 64
- Treatment guidelines 64

## Evidence scores

## References

## Images

## Disclaimer
Summary

- Progressive disease state characterised by airflow limitation that is not fully reversible.
- Suspected in patients with a history of smoking, occupational and environmental risk factors, or a personal or family history of chronic lung disease.
- Presents with progressive shortness of breath, wheeze, cough, and sputum production, including haemoptysis.
- Diagnostic tests include PFTs, CXR, chest CT scan, oximetry, and ABG analysis.
- Patients should be encouraged to stop smoking or occupational exposure and be vaccinated against viral influenza and Streptococcus pneumoniae.
- Treatment options include bronchodilators, inhaled corticosteroids, and systemic corticosteroids.
- Long-term oxygen therapy improves survival in severe COPD.
Definition

COPD is a preventable and treatable disease state characterised 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 aged 65 years and older. The Burden of Obstructive Lung Disease (BOLD) Initiative estimates a worldwide population prevalence of COPD for stages II or higher as equivalent to 10.1 ± 4.8% overall with 11.8 ± 7.9% for men and 8.5 ± 5.8% for women.[4] Its 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. In 2002, the WHO stated that COPD had become the fifth leading cause of death and disability worldwide,[5] and it is now projected to be the third leading cause of death in the world by 2020.[1] [5] This is because of the expanding epidemic of smoking and ageing of the world population and reduced mortality from other causes of death like cardiovascular disease.[1] [6] A retrospective study conducted in the UK between 1990 and 1997 estimated COPD prevalence to be 2% in men and 1% in women.[7]

Aetiology

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 aetiologies. 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 remodelling 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 pathological 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.

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 physiological 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][11]
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 counselling. Although smoking cessation may be associated with minor short-term adverse effects such as weight gain and constipation, its long-term benefits are unquestionable.[18] 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.[23] 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.[24]

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 CXR or CT 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.[136] [137] 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.[138] 8[A]Evidence 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.[113]

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 one 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 oedema.

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 rhinorrhoea. 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 haemoptysis, chills, or weight loss and has not received any relief from over-the-counter cough preparations.

Other presentations

Other presentations include weight loss, haemoptysis, cyanosis, and morning headaches secondary to hypercapnia. Physical examination may demonstrate hypoxia, use of accessory muscles, paradoxical rib movements, distant heart sounds, lower-extremity oedema 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, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, and lung cancer.[1]

Step-by-step diagnostic approach

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.
Physical examination
Examination may show tachypnoea, respiratory distress, use of accessory muscles, and intercostal retraction. Barrel chest is a common observation. There may be hyper-resonance on percussion, and distant breath sounds and poor air movement on auscultation. Wheezing, coarse crackles, clubbing, and cyanosis, as well as signs of right-sided heart failure (distended neck veins, loud P2, hepatomegaly, hepatojugular reflux, and lower-extremity oedema), 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, stable disease
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 post-bronchodilator FEV1/FVC <0.70.[1] In cases where FVC may be hard to measure, forced expiratory volume at 6 seconds (FEV6) can be used.[19] Chest x-ray (CXR) is rarely diagnostic but can help to exclude other diagnoses. Pulse oximetry screens for hypoxia.

In addition to airflow limitation, the GOLD guidelines recognise 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.

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

Initial tests, acute exacerbation
Patients presenting with acute symptoms should have FBC, ECG, CXR, and assessment of gas exchange (pulse oximetry and/or ABG analysis).[1] Spirometry is not recommended in an acute exacerbation as it may be hard to perform and not very accurate.[1]
**Other tests**

Presence of purulent sputum is sufficient to commence empirical antibiotics in an acute exacerbation. If these fail, sputum should be sent for culture.[1]

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. 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.[1] This may aid in family screening and counselling.

CT scans show anatomical 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 apnoea is associated with increased risk of death and hospitalisation in patients with COPD.[20]

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

[VIDEO: Radial artery puncture animated demonstration ]

**Risk factors**

**Strong**

**cigarette smoking**

- Most important risk factor. It causes 40% to 70% of cases of COPD.[12]
- 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.
COPD

Diagnosis

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 sulphur dioxide increases risk of COPD.

developmentally abnormal lung

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

male gender

- 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.[13] [14] [15] [16]

low socio-economic status

- The risk for developing COPD is increased in people with lower socio-economic status.[17] However, this may reflect exposure to cigarette smoke, pollutants, or other factors.

History & examination factors

Key diagnostic factors

presence of risk factors (e.g., smoking) (common)

- The main risk factor is smoking. Other key risk factors include advancing age and genetic 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.

hyper-resonance on percussion (common)

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

distant breath sounds on auscultation (common)
COPD

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

**poor air movement on auscultation (common)**
• Secondary to loss of lung elasticity and lung tissue breakdown.

**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 over-secretion.

**tachypnoea (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)**

• Clubbing is usually not present until significant impairment of lung function has occurred.

# Diagnostic tests

## 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td>FEV1/FVC ratio &lt;0.70; total absence of reversibility is neither required nor the most typical result</td>
</tr>
<tr>
<td><strong>Pulse oximetry</strong></td>
<td>low oxygen saturation</td>
</tr>
<tr>
<td><strong>ABG</strong></td>
<td>PaCO2 &gt;50 mmHg and/or PaO2 of &lt;60 mmHg suggests respiratory insufficiency</td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>hyperinflation</td>
</tr>
<tr>
<td><strong>FBC</strong></td>
<td>raised haematocrit, possible increased WBC count</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>signs of right ventricular hypertrophy, arrhythmia, ischaemia</td>
</tr>
</tbody>
</table>

- 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.

- 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.

- Hypercapnia, hypoxia, and respiratory acidosis are signs of impending respiratory failure and possible need for intubation.

- 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.

- Risk factors for COPD are similar to those for ischaemic heart disease, so comorbidity is common.
## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sputum culture</strong></td>
<td>• Presence of purulent sputum is sufficient to commence empirical antibiotics. Sputum culture indicated if empirical antibiotics fail.[1]</td>
</tr>
<tr>
<td><strong>PFTs</strong></td>
<td>• Useful for resolving diagnostic uncertainties and preoperative assessment.[1] Requires specialist laboratory facilities. • Decreased diffusing capacity of the lung for carbon monoxide (DLCO) is supportive of emphysema over chronic bronchitis.</td>
</tr>
<tr>
<td><strong>chest CT scan</strong></td>
<td>• Provides better visualisation of type and distribution of lung tissue damage and bulla formation than CXR. [Fig-3] • In contrast to smoking-related COPD, alpha-1 antitrypsin deficiency mainly affects lower fields. • Useful in excluding other underlying pulmonary disease and for preoperative assessment.</td>
</tr>
<tr>
<td><strong>alpha-1 antitrypsin level</strong></td>
<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 non-smokers).</td>
</tr>
<tr>
<td><strong>exercise testing</strong></td>
<td>• Can be of value in patients with a disproportional degree of dyspnoea 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). Exercise testing is of use in selecting patients for rehabilitation.</td>
</tr>
<tr>
<td><strong>sleep study</strong></td>
<td>• Obstructive sleep apnoea, a common finding in patients with COPD, is associated with increased risk of death and hospitalisation in patients with COPD.[20]</td>
</tr>
<tr>
<td><strong>respiratory muscle function</strong></td>
<td>• Respiratory muscle function may be tested if dyspnoea or hypercapnia are disproportionately increased with respect to FEV1, as well as in patients with poor nutrition and those with corticosteroid myopathy.[22]</td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>• Onset of asthma is usually in early life. A personal or family hx 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>• 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>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>• Usually a history of cardiovascular diseases is present. Patients report symptoms of orthopnoea, 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>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Tuberculosis</td>
<td>• A history of fever, night sweats, weight loss, and chronic productive cough is usually present. Tuberculosis is more common in immigrants to non-endemic countries, and in people living in endemic countries.</td>
<td>• The diagnosis requires microbiological confirmation. Infiltrates, fibrosis, or granuloma seen on CXR or chest CT may suggest tuberculosis. Patients usually have positive skin test for tuberculosis.</td>
</tr>
<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 post-infectious.</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>Condition</td>
<td>Differentiating signs / symptoms</td>
<td>Differentiating tests</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Upper airway dysfunction</td>
<td>• Can affect patients of any age. History of prior trauma 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>• The flow-volume curve in pulmonary function testing may reveal a characteristic expiratory or inspiratory plateau, or both. Diagnosis is confirmed by direct visualisation of the affected airway by endoscopy.</td>
</tr>
<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, non-productive cough, and/or headache.</td>
<td>• CT of sinuses and/or empirical trial of antihistamines is commonly utilised to aid in diagnosis.</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux disease (GORD)</td>
<td>• Patients with GORD 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 empirical therapy with proton-pump inhibitors.</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>• ACE inhibitors can cause chronic cough; however, the cough is usually non-productive.</td>
<td>• Diagnosis is usually based on improvement of symptoms after empirical cessation of ACE inhibitor.</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>• Patients may have weight loss, night sweats, haemoptysis, 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 post-bronchodilator FEV1/FVC ratio of <0.70 is commonly considered diagnostic for COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) system categorises airflow limitation into stages. In patients with FEV1/FVC <0.70:

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

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

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

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.[1] There is a stepwise approach to therapy, but it is important to remember that treatment should be individualised for general health status and comorbid conditions.

The therapeutic approach involves reducing risk factor exposure, appropriate assessment of disease, patient education, pharmacological and non-pharmacological 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 well-being will improve, and hospital admissions will be significantly decreased in cases where self- or professional monitoring of disease is being utilised.[25] Such assessment of the medical history should include:

Exposure to risk factors and preventative 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 department visits
- Recent oral corticosteroid bursts
- Frequency, severity, and likely causes of exacerbations should be evaluated.

Comorbidities:

- Assessment of co-existing 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 (physiotherapist, respiratory physician, nurse, etc.) worked together with patients has been shown to improve quality of life and decrease hospital admissions.[26]

**Acute exacerbations**

An exacerbation of COPD is defined as an event characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations and is acute in onset.

Patients can be treated either as inpatients or as outpatients, depending on severity of symptoms and comorbidities. Indications for hospitalisation include significant comorbidities (heart failure, arrhythmias, kidney disease), failure of outpatient treatment, worsening gas exchange, or an inability to cope at home.[1]

ICU admission is considered for patients with worsening respiratory function (hypoxaemia or hypercapnia), severe respiratory acidosis, or haemodynamic instability, and those requiring mechanical ventilation.[1] Use of non-invasive positive airway pressure (NIPAP) and/or mechanical ventilation may be inevitable in severe cases of COPD exacerbations.[27] [28]

Infections are among the most common causes of COPD exacerbation. The use of empirical antibiotics in suspected cases of infection is usually warranted because it has beneficial effects on lung function and duration of disease, as well as potential benefit for dyspnoea, cough, and sputum purulence, especially for patients admitted to the ICU.[29] [30] Choice of antibiotic should be made according to severity of exacerbation and whether or not the patient is being treated in hospital.[29] [31] [32] [33]

Bronchodilators are indicated, with or without supplemental oxygen. Oral corticosteroids should also be considered.[1] A short course (i.e., usually 5 days) of corticosteroid therapy appears to be as effective as a 10- to 14-day course.[34] [35] When needed for treatment of an exacerbation, oral or parenteral therapy is superior to inhaled corticosteroids.[36] [37] A 5-day course of oral prednisolone (40 mg/day) is recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[1] There is no evidence that parenteral treatment is better than oral therapy with regards to relapse, treatment failure, or mortality. There is a greater risk of side effects with parenteral therapy.[37]

**Stepwise therapy according to GOLD class**

GOLD guidelines[1] recommend a stepwise approach to pharmacological 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.1[A]Evidence
- 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.2[A]Evidence

### Bronchodilator therapy options

Beta agonists are widely used in the treatment of COPD.3[A]Evidence 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.[38]

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.4[B]Evidence Inhaled muscarinic antagonists are available as both short- and long-acting preparations. There is a suggestion of increased cardiovascular-related mortality in retrospective studies of patients taking short-acting inhaled muscarinic antagonists. There is no increase in cardiovascular-related events in patients taking long-acting muscarinic antagonists (LAMA).[39]

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.[40] [41] [42] [43] 1[A]Evidence

In cases of stable COPD, if the decision is made to use single-agent therapy, LAMA may be superior to LABA agents.[40] Clinical trials have shown that LAMA have a greater effect on reducing rates of exacerbations compared with LABA.[44] [45] The long-term safety of LAMA was demonstrated in the UPLIFT trial.[46] As outlined above, GOLD makes recommendations on the initial agent based on the patient’s risk group (A, B, C, or D).[1]

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.5[A]Evidence Theophylline has modest effects on lung function in moderate-to-severe COPD.[47]

Umeclidinium/vilanterol is a combination of a long-acting beta-2 agonist and a long-acting muscarinic antagonist (LABA/LAMA) approved for use in COPD.[48] Glycopyrronium/formoterol fumarate is another LABA/LAMA combination approved for COPD patients,[49] as is indacaterol/glycopyrronium.[50] [51] This once-daily inhaler showed superior efficacy compared with glycopyrronium plus tiotropium in patients with moderate to severe COPD,[52] and compared with salmeterol/fluticasone in preventing COPD exacerbation.[53]

### Inhaled corticosteroids

Inhaled corticosteroids are indicated in patients with advanced stages of COPD who suffer from frequent exacerbations.[54] They should be added to the patient's existing bronchodilator therapy and should not be used as monotherapy.[1] 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.[55] [56] Several studies have pointed to an increased risk of pneumonia in COPD patients taking inhaled corticosteroids.[57] This risk is slightly higher for fluticasone in comparison with budesonide.[58] Therefore, an individualised treatment approach that assesses a patient’s risk of pneumonia versus the benefit of decreased exacerbations should be implemented.[57] [59] [60] Concern is also raised with regards to increased risk of TB and influenza in adult patients with COPD who are on inhaled corticosteroid therapy.[61]

According to the 2017 GOLD guidelines, 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.[1]

**Phosphodiesterase-4 inhibitors**

Roflumilast is a phosphodiesterase-4 inhibitor that may reduce exacerbations in group D patients at risk for frequent exacerbations when not adequately controlled by long-acting bronchodilators.[1] 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.[62]

**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. 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.

**Patient education**

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.

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

**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 programmes include counselling, group meetings, and drug therapy.[65] Some patients may need frequent referrals to achieve success. Smoking cessation significantly reduces the rate of progression of COPD and risk of malignancies.[2][Evidence] It also reduces risk of coronary and cerebrovascular diseases. Smoking cessation that includes pharmacotherapy and intensive counselling has a higher success rate and is cost effective in COPD, with low costs per quality-adjusted life year.[66] [67]

Patients should be vaccinated against influenza virus and *Streptococcus pneumoniae*. [1] [68] Vaccination against influenza is associated with fewer exacerbations of COPD.[69] [68]
**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.[70] 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 hospitalisations or rate of exacerbations.[71]

**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 hospitalisation in COPD patients.[72] The benefit appears to subside after termination of the course unless patients follow a home exercise schedule.[73] Benefits of home-based pulmonary rehabilitation on respiratory symptoms and quality of life in patients with COPD could match those of the hospital-based rehabilitation programmes.[74] Although pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent,[75] it is important to remember that early progressive exercise rehabilitation beyond current standard physiotherapy practice during hospital admission for COPD is not recommended and could be associated with a higher 12-month mortality.[76] There is evidence to support starting pulmonary rehabilitation within 1 month of an acute exacerbation.[77]

GOLD guidelines recommend pulmonary rehabilitation for patient groups B to D.[1]

**Oxygen therapy**

GOLD guidelines recommend long-term oxygen therapy in stable patients who have:[1]

- 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 oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit > 55%).

Oxygen therapy helps to minimise pulmonary hypertension by decreasing pulmonary artery pressure, and improves exercise tolerance and quality of life. It has been shown to improve survival.[1] [78] [79]

Evidence

Oxygen is suggested for patients in whom the predicted PaO2 during air travel is <6.7 kPa (<50 mmHg).[1] 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.

**Surgery**

Surgical interventions (bullectomy, lung volume reduction surgery, 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.[80]
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.[81] 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.[82]

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

<table>
<thead>
<tr>
<th>Acute</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute exacerbation</td>
<td>1st short-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td>adjunct transition to inhaled corticosteroid</td>
</tr>
<tr>
<td></td>
<td>adjunct supplemental oxygen</td>
</tr>
<tr>
<td>infectious exacerbation</td>
<td>plus oral antibiotic</td>
</tr>
<tr>
<td>outpatients</td>
<td></td>
</tr>
<tr>
<td>infectious exacerbation</td>
<td>plus oral or systemic antibiotics</td>
</tr>
<tr>
<td>hospitalised patients</td>
<td></td>
</tr>
<tr>
<td>respiratory insufficiency</td>
<td>adjunct non-invasive positive-pressure ventilation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>group A: few symptoms and low risk of exacerbations</td>
<td>1st short- or long-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td>plus patient education and vaccination</td>
</tr>
<tr>
<td></td>
<td>plus smoking cessation</td>
</tr>
</tbody>
</table>

| group B: more symptoms and low risk of exacerbations | 1st long-acting bronchodilator |
| | plus short-acting bronchodilator as required |
| | plus patient education and vaccination |
| | plus smoking cessation |
## COPD Treatment

### Ongoing

<table>
<thead>
<tr>
<th></th>
<th>Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pulmonary rehabilitation</td>
</tr>
<tr>
<td>adjunct</td>
<td>long-term oxygen therapy</td>
</tr>
</tbody>
</table>

#### 2nd dual long-acting bronchodilator therapy

<table>
<thead>
<tr>
<th></th>
<th>Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>short-acting bronchodilator as required</td>
</tr>
<tr>
<td></td>
<td>patient education and vaccination</td>
</tr>
<tr>
<td></td>
<td>smoking cessation</td>
</tr>
</tbody>
</table>

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

#### 1st long-acting bronchodilator

<table>
<thead>
<tr>
<th></th>
<th>Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>short-acting bronchodilator as required</td>
</tr>
<tr>
<td></td>
<td>patient education and vaccination</td>
</tr>
<tr>
<td></td>
<td>smoking cessation</td>
</tr>
</tbody>
</table>

#### adjunt long-term oxygen therapy

<table>
<thead>
<tr>
<th></th>
<th>Adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>theophylline or aminophylline</td>
</tr>
</tbody>
</table>

#### 2nd dual long-acting bronchodilator therapy

<table>
<thead>
<tr>
<th></th>
<th>Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>short-acting bronchodilator as required</td>
</tr>
<tr>
<td></td>
<td>patient education and vaccination</td>
</tr>
<tr>
<td></td>
<td>smoking cessation</td>
</tr>
</tbody>
</table>

### adjunt long-term oxygen therapy

<table>
<thead>
<tr>
<th></th>
<th>Adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>theophylline or aminophylline</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>short-acting bronchodilator as required</td>
</tr>
<tr>
<td></td>
<td>patient education and vaccination</td>
</tr>
<tr>
<td></td>
<td>smoking cessation</td>
</tr>
</tbody>
</table>

### adjunt long-term oxygen therapy

<table>
<thead>
<tr>
<th></th>
<th>Adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>theophylline or aminophylline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>long-term oxygen therapy</td>
</tr>
</tbody>
</table>
## Ongoing

**group D: more symptoms and high risk of exacerbations**

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

*This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Jun 28, 2018. BMJ Best Practice topics are regularly updated and the most recent version of the topics can be found on bestpractice.bmj.com. Use of this content is subject to our disclaimer. © BMJ Publishing Group Ltd 2018. All rights reserved.*
<table>
<thead>
<tr>
<th>Ongoing</th>
<th>( summary )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>adjunct</td>
</tr>
</tbody>
</table>
## Treatment options

### Acute

#### acute exacerbation

<table>
<thead>
<tr>
<th>1st</th>
<th>short-acting bronchodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
</tbody>
</table>
| » **salbutamol inhaled:** 2.5 to 5 mg nebulised every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing; (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing  
- **and/or-**  
» ipratropium inhaled: 0.25 to 0.5 mg nebulised every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing; (20 micrograms/dose inhaler) 40 micrograms (2 puffs) every 20 minutes for up to 2 hours or until clinical improvement, followed by 4-6 hourly dosing |

| Patients may need an increased dose or frequency of dosing in an exacerbation, compared with their usual maintenance doses. |

| Other delivery devices such as a spacer or nebuliser can be considered to optimise drug delivery.[1] Nebulised delivery is preferred. |

| Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[83] [84] |

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

<table>
<thead>
<tr>
<th>2nd</th>
<th>systemic corticosteroid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
</tbody>
</table>
| » **prednisolone:** 30-60 mg orally once daily for 5 days  
**OR**  
» methylprednisolone: 40-60 mg/day orally given once daily or in 2 divided doses for 5-7 days |
## Acute

» In severe but not life-threatening exacerbations, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend considering a short course of oral corticosteroids.[1]

» During acute exacerbations, systemic corticosteroids are superior to inhaled corticosteroids, and their use usually spares the use of inhaled corticosteroids.

» The oral route is preferred. It is not known whether tapering systemic corticosteroids provides clinical benefit apart from likely avoidance of adrenal insufficiency.

» A short course (i.e., usually 5 days) of corticosteroid therapy appears to be as effective as a 10- to 14-day course.[34] [35] A 5-day course of oral prednisolone (40 mg/day) is recommended by the GOLD guidelines.[1]

There is no evidence that parenteral treatment is better than oral therapy with regards to relapse, treatment failure, or mortality. There is a greater risk of side effects with parenteral therapy.[37]

» When acute exacerbations are under control, patients can be started on inhaled corticosteroids (if indicated), with a few days of overlap.[85] [86]

### transition to inhaled corticosteroid

#### adjunct

**Primary options**

- **beclometasone inhaled:** (50 or 100 micrograms/dose metered-dose inhaler) 100-250 micrograms/day

OR

- **budesonide inhaled:** (100, 200, or 400 micrograms/dose inhaler) 200-600 micrograms/day given in 2 divided doses

OR

- **flunisolide inhaled:** (250 micrograms/dose inhaler) 500-1000 micrograms/day given in 2 divided doses

OR

- **fluticasone propionate inhaled:** (50, 100, 250 micrograms/dose inhaler) 100-500 micrograms twice daily

OR
**Acute**

- **mometasone inhaled**: (220 micrograms/dose inhaler) 220-440 micrograms (1-2 puffs) once daily

- For patients in group C or D, an acute exacerbation may indicate the need to escalate long-term therapy to a regimen containing inhaled corticosteroids.

- Inhaled corticosteroids have been shown to improve airflow in patients with acute exacerbations of COPD when compared with placebo.\[87\] They are generally well tolerated. The optimal dose of inhaled corticosteroids in COPD is unknown; moderate to high doses have been used in clinical trials evaluating the impact of inhaled corticosteroids in COPD.\[1\]

- Inhaled corticosteroids may be associated with side effects similar to systemic corticosteroids when used long term.

- Higher doses of inhaled corticosteroids are used during transition from systemic to inhaled corticosteroid therapy or in mild exacerbation, compared with maintenance dose.

**adjunct airway clearance techniques**

- Selected airway clearance techniques such as mechanical vibration and non-oscillating positive expiratory pressure may improve sputum clearance in some patients with copious secretions, or concurrent bronchiectasis, and may slightly reduce short-term risk of need for ventilatory assistance.\[88\] but are not uniformly helpful.\[71\] Other clearance techniques such as manual chest wall percussion are also either not routinely helpful or may have detrimental effects.\[89\] \[90\] \[91\] There is no proven benefit of airway clearance techniques on long-term outcomes following COPD exacerbation, such as reduction in subsequent exacerbation risk.\[88\]

**adjunct supplemental oxygen**

- Gas exchange should be monitored with ABGs 30 minutes after commencing supplemental oxygen therapy, as carbon dioxide retention may occur. Suplemental oxygen should be titrated to improve the patient's hypoxaemia with a target saturation [SaO2] of 88% to 92%.\[1\]

**infectious exacerbation outpatients**

- **oral antibiotic**

**Primary options**
### Acute

- **doxycycline**: 100 mg orally twice daily for 5-10 days
  
  OR

- **tetracycline**: 250-500 mg orally four times daily for 5-7 days
  
  OR

- **amoxicillin**: 250-500 mg orally three times daily for 5-10 days
  
  OR

- **amoxicillin/clavulanate**: 500 mg orally every 8 hours, or 875 mg orally every 12 hours for 5-10 days  
  Dose refers to amoxicillin component
  
  OR

- **cefaclor**: 250-500 mg orally three times daily for 5-10 days
  
  OR

- **azithromycin**: 500 mg orally as a single dose on day 1, followed by 250 mg once daily on days 2-5
  
  OR

- **clarithromycin**: 250-500 mg orally twice daily for 7-14 days
  
  OR

- **telithromycin**: 800 mg orally once daily for 7-10 days
  
  **Secondary options**

- **levofloxacin**: 500 mg orally once daily for 5-7 days
  
  OR

- **moxifloxacin**: 400 mg orally once daily for 5 days
  
  OR
<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» <strong>ciprofloxacin</strong>: 250-500 mg orally twice daily for 5-10 days</td>
</tr>
<tr>
<td></td>
<td>» According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnoea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or non-invasive). The recommended length of antibiotic therapy is 5 to 7 days.[1]</td>
</tr>
<tr>
<td></td>
<td>» Empirical antibiotics should be commenced to cover common infecting organisms: <em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, and <em>Moraxella</em> spp. Amoxicillin is not appropriate in areas where there is increased prevalence of beta-lactamase-producing <em>Haemophilus influenzae</em>, <em>Moraxella catarrhalis</em>, or <em>Streptococcus pneumoniae</em> resistant to penicillin. Fluoroquinolones are second-line therapy except in cases of severe infections in high-risk patients who require hospitalisation or broad-spectrum coverage. The fluoroquinolones gatifloxacin and moxifloxacin are suitable options if available.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>infectious exacerbation</strong> plus <strong>hospitalised patients</strong></td>
</tr>
<tr>
<td></td>
<td><strong>oral or systemic antibiotics</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
<tr>
<td></td>
<td>» <strong>ceftriaxone</strong>: 1 g intravenously every 12 hours for 5-10 days</td>
</tr>
<tr>
<td></td>
<td>-or-</td>
</tr>
<tr>
<td></td>
<td>» <strong>piperacillin/tazobactam</strong>: 3.375 g intravenously given every 6 hours for 7-10 days</td>
</tr>
<tr>
<td></td>
<td>Dose consists of 3 g of piperacillin and 0.375 g of tazobactam.</td>
</tr>
<tr>
<td></td>
<td>-or-</td>
</tr>
<tr>
<td></td>
<td>» <strong>meropenem</strong>: 500-1000 mg intravenously every 8 hours for 7-10 days</td>
</tr>
<tr>
<td></td>
<td><strong>-AND--</strong></td>
</tr>
<tr>
<td></td>
<td>» <strong>azithromycin</strong>: 500 mg orally as a single dose on day 1, followed by 250 mg once daily on days 2-5</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary options</strong></td>
</tr>
<tr>
<td></td>
<td>» <strong>levofloxacin</strong>: 500 mg orally/intravenously once daily for 5-7 days</td>
</tr>
</tbody>
</table>
|       | **OR**
### TREATMENT

#### COPD

**Acute**

- **moxifloxacin**: 400 mg orally/intravenously once daily for 5-14 days

**Tertiary options**

- **ciprofloxacin**: 250-500 mg orally twice daily for 5-10 days

According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnoea, sputum volume, and sputum purulence; have two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or non-invasive). The recommended length of antibiotic therapy is 5 to 7 days.\(^1\)

- Ceftriaxone is used as inpatient therapy with azithromycin for severe infection (as an alternative to fluoroquinolones). Piperacillin plus tazobactam, or meropenem, are first-line for inpatient therapy in high-risk people (individuals >65 years, recent and/or prolonged hospitalisation, poor functional status, or those who have had recent and prolonged use of antibiotics), especially if there is suspicion of *Pseudomonas* infections.

- Fluoroquinolones are second-line therapy except in cases of severe infections in high-risk patients who require hospitalisation or broad-spectrum coverage. Levofloxacin has better coverage than ciprofloxacin for gram-positive organisms. The fluoroquinolones gatifloxacin and moxifloxacin are suitable options if available.

**respiratory insufficiency**

**adjunct**

**non-invasive positive-pressure ventilation**

- Respiratory failure is often seen in patients with severe acute exacerbations of COPD. The application of non-invasive positive-pressure ventilation (NPPV) has been shown to improve gas exchange, reduce dyspnoea, decrease the need for endotracheal intubation, reduce complications, and decrease length of hospitalisation and mortality in these patients.\(^1\)\(^2\)\(^8\)\(^9\)\(^2\)\(^9\)\(^3\)\(^4\)\(^5\) NPPV use should be considered for patients with at least one of the following: respiratory acidosis (pH ≤7.35) and/or hypercapnia (PaCO2 ≥45 mmHg); severe dyspnoea with use of accessory respiratory muscles, paradoxical movement of the abdomen with respiration, or retraction of the intercostal spaces; or persistent hypoxaemia despite supplemental oxygen therapy.\(^1\)
Acute

» Improvements in patient’s level of dyspnoea and their physiological state are typically seen within 1 to 4 hours. However, NPPV is not successful for all patients, and clinicians should discuss the risks and benefits of invasive mechanical ventilation with patients receiving NPPV to determine their desired course of treatment.

adjunct invasive positive-pressure ventilation

» If non-invasive positive-pressure ventilation (NPPV) fails, invasive mechanical ventilation should be considered. This is particularly true for patients with altered mental status and worsening respiratory status; patients at risk for aspiration; or if NPPV can not be used, such as in facial trauma.

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

Ongoing

group A: few symptoms and low risk of exacerbations

1st short- or long-acting bronchodilator

Primary options

» salbutamol inhaled: (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required

OR

» ipratropium inhaled: (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required

OR

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

OR
COPD Treatment

Ongoing

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

OR

» **arformoterol inhaled**: 15 micrograms nebulised 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

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

» **glycopyrronium inhaled**: (50 micrograms/capsule inhaler) 50 micrograms (1 capsule) once daily

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.\[1\]

» 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.\[1\]

» Short-acting bronchodilators provide symptomatic relief.\[7][A]\ Evidence

» Failure to respond to short-acting bronchodilator may signify an acute exacerbation.\[83] [84]
**Ongoing**

> Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[83] [84]

> Short-acting drugs include salbutamol and ipratropium.

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

**Plus** patient education and vaccination

> Influenza and pneumococcal vaccination should be offered to every COPD patient.[1] 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%.[102]

> Patients should be well educated about the disease course and symptoms of exacerbation or decompensation.

> 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.[81]

**Plus** smoking cessation

> 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.[2][A]Evidence

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

---

**Group B: More symptoms and low risk of exacerbations**

**1st long-acting bronchodilator**

**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
Ongoing

- arformoterol inhaled: 15 micrograms nebulised 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

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

- glycopyrronium inhaled: (50 micrograms/ capsule inhaler) 50 micrograms (1 capsule) once daily

- Long-acting muscarinic antagonists (LAMA) or long-acting beta-2 agonists (LABA)\(^1\) can be used as first-line therapy in this group of patients.\(^1\)

- 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.\(^{1,104,105}\)

- 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.\(^1\)

- For patients with severe breathlessness, initial therapy with two bronchodilators may be considered.\(^1\)
## Ongoing

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» For patients with persistent breathlessness on monotherapy, GOLD guidelines recommend the use of two bronchodilators.[1]</td>
</tr>
<tr>
<td></td>
<td>» Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[83] [84]</td>
</tr>
</tbody>
</table>

**plus short-acting bronchodilator as required**

### Primary options

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» salbutamol inhaled: (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>» ipratropium inhaled: (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required</td>
</tr>
</tbody>
</table>

**plus patient education and vaccination**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» Influenza and pneumococcal vaccination should be offered to every COPD patient.[1] 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%. [102]</td>
</tr>
<tr>
<td></td>
<td>» Patients should be well educated about the disease course and symptoms of exacerbation or decompensation.</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.[81]</td>
</tr>
</tbody>
</table>

**plus smoking cessation**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<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. [2][A] Evidence</td>
</tr>
</tbody>
</table>
Ongoing

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

plus pulmonary rehabilitation

» Pulmonary rehabilitation should be started early.[1]

» 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 dyspnoea, exercise ability, health status, and healthcare utilisation.[1] [78]

adjunct long-term oxygen therapy

» 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 oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit >55%).[1]

» Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg).[1] 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.[78] [80] 6[B]Evidence

2nd dual long-acting bronchodilator therapy

Primary options

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

OR

» glycopyrronium/formoterol fumarate inhaled: (14.4/9.6 micrograms/dose inhaler) 1 puff twice daily
## Ongoing

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>» <strong>indacaterol/glycopyrronium inhaled:</strong></td>
<td>(110/50 micrograms/capsule inhaler) 1 capsule once daily</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» <strong>tiotropium/olodaterol inhaled:</strong></td>
<td>(2.5/2.5 micrograms/dose inhaler) 2 puffs once daily</td>
</tr>
<tr>
<td>» For patients with persistent breathlessness on monotherapy, Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of two bronchodilators.[1]</td>
<td></td>
</tr>
<tr>
<td>» If two bronchodilators do not improve symptoms, GOLD guidelines suggest stepping down again to a single bronchodilator.[1]</td>
<td></td>
</tr>
<tr>
<td>» Umeclidinium/vilanterol, glycopyrronium/ formoterol fumarate,[49] indacaterol/ glycopyrronium,[53] 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.[48]</td>
<td></td>
</tr>
<tr>
<td>plus</td>
<td><strong>short-acting bronchodilator as required</strong></td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» <strong>salbutamol inhaled:</strong></td>
<td>(100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» <strong>ipratropium inhaled:</strong></td>
<td>(20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required</td>
</tr>
<tr>
<td>» Provides symptomatic relief.[7][A]Evidence</td>
<td></td>
</tr>
<tr>
<td>» Failure to respond to short-acting bronchodilator may signify an acute exacerbation.</td>
<td></td>
</tr>
<tr>
<td>» Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[83][84]</td>
<td></td>
</tr>
<tr>
<td>plus</td>
<td><strong>patient education and vaccination</strong></td>
</tr>
<tr>
<td>» <strong>Influenza and pneumococcal vaccination</strong> should be offered to every COPD patient.[1] 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</td>
<td></td>
</tr>
</tbody>
</table>
Ongoing treatment of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%.\[102\]

» Patients should be well educated about the disease course and symptoms of exacerbation or decompensation.

» 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.\[81\]

plus smoking cessation

» 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.\[2\][A]Evidence

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

plus pulmonary rehabilitation

» Pulmonary rehabilitation should be started early.\[1\]

» 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 dyspnoea, exercise ability, health status, and healthcare utilisation.\[1\] \[78\]

adjunct long-term oxygen therapy

» 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 oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit >55%).\[1\]

» Oxygen is suggested for patients in whom the predicted PaO2 during air travel is <6.7 kPa (<50 mmHg).\[1\] 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.
Ongoing

In addition, oxygen saturation should stay above 90% during rest, exercise, and sleep. Evidence

**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

- **glycopyrronium inhaled**: (50 micrograms/capsule inhaler) 50 micrograms (1 capsule) once daily

  Initial treatment in group C should be a single long-acting bronchodilator. 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. 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.

**plus short-acting bronchodilator as required**

**Primary options**

- **salbutamol inhaled**: (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required

  OR
Ongoing

- ipratropium inhaled: (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required

- Provides symptomatic relief. [7A] Evidence

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

- Patients should not take short-acting anticholinergic agents (e.g., ipratropium) if they have already been started on tiotropium. [83] [84]

**plus** patient education and vaccination

- Influenza and pneumococcal vaccination should be offered to every COPD patient. [1]
  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%. [102]

- Patients should be well educated about the disease course and symptoms of exacerbation or decompensation.

- 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. [81]

**plus** smoking cessation

- 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. [2A] Evidence

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

**plus** pulmonary rehabilitation

- Pulmonary rehabilitation should be started early. [1]

- 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 dyspnoea, exercise, quality of life, and emotional feelings. [1] [78]
COPD

Treatment

Ongoing

**adjunct** theophylline or aminophylline

**Primary options**

- **theophylline**: 300 mg/day orally 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

OR

- **aminophylline**: consult specialist for guidance on dose

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

- Toxicity is dose-related.5[A]Evidence

**adjunct long-term oxygen therapy**

- 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 oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit >55%).[1]

- Oxygen is suggested for patients in whom the predicted PaO2 during air travel is <6.7 kPa (<50 mmHg).[1] 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.[78] [80] 6[B]Evidence

2nd **dual long-acting bronchodilator therapy**

**Primary options**

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

OR
**COPD**

**Treatment**

**Ongoing**

» **glycopyrronium/formoterol fumarate inhaled:** (14.4/9.6 micrograms/dose inhaler) 1 puff twice daily

OR

» **indacaterol/glycopyrronium inhaled:** (110/50 micrograms/capsule inhaler) 1 capsule once daily

OR

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

» 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).

» Umeclidinium/vilanterol, glycopyrronium/formoterol fumarate,[49] indacaterol/glycopyrronium,[53] and tiotropium/olodaterol are combinations of a LABA and a LAMA approved for use in COPD.[48]

**plus** short-acting bronchodilator as required

**Primary options**

» **salbutamol inhaled:** (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required

OR

» **ipratropium inhaled:** (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required

» Provides symptomatic relief.[7][A]Evidence

» 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.[83] [84]

**plus** patient education and vaccination

» Influenza and pneumococcal vaccination should be offered to every COPD patient.[1] 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...
Ongoing conditions. This vaccine also reduces incidence of community-acquired pneumonia in patients younger than 65 with an FEV1 of <40%.[102]

» Patients should be well educated about the disease course and symptoms of exacerbation or decompensation.

» 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.[81]

plus smoking cessation

» 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.2[A]Evidence

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

plus pulmonary rehabilitation

» Pulmonary rehabilitation should be started early.[1]

» 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 dyspnoea, exercise, quality of life, and emotional feelings.[1] [78]

adjunct theophylline or aminophylline

Primary options

» theophylline: 300 mg/day orally 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

OR

» aminophylline: consult specialist for guidance on dose

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

» Toxicity is dose-related.5[A]Evidence
adjunct long-term oxygen therapy

» 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 oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit >55%).[1]

» Oxygen is suggested for patients in whom the predicted PaO2 during air travel is <6.7 kPa (<50 mmHg).[1] 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.[78] [80]

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 increase the risk of developing pneumonia in...
### COPD Treatment

#### Ongoing

Some patients, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines prefer dual long-acting bronchodilator therapy over a LABA/ICS combination.[1]

- 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

#### Primary options

- **salbutamol inhaled:** (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required

  OR

- **ipratropium inhaled:** (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required

  » Provides symptomatic relief. Evidence

  » 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.[83] [84]

**plus** patient education and vaccination

- Influenza and pneumococcal vaccination should be offered to every COPD patient.[1] 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%.[102]

  » Patients should be well educated about the disease course and symptoms of exacerbation or decompensation.

  » Discussions should be held early in the course of the disease, before acute respiratory failure
<table>
<thead>
<tr>
<th>Ongoing</th>
<th>COPD Treatment develops, about the possible need for and benefits of palliative care in the future.[81]</th>
</tr>
</thead>
<tbody>
<tr>
<td>plus</td>
<td><strong>smoking cessation</strong></td>
</tr>
<tr>
<td></td>
<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.[2][Evidence]</td>
</tr>
<tr>
<td></td>
<td>» Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate non-pharmacological therapies, should be used.</td>
</tr>
<tr>
<td>plus</td>
<td><strong>pulmonary rehabilitation</strong></td>
</tr>
<tr>
<td></td>
<td>» Pulmonary rehabilitation should be started early.[1]</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 improvements in multiple outcome areas, including dyspnoea, exercise capacity, quality of life, and emotional feelings.[1][78]</td>
</tr>
<tr>
<td>adjunct</td>
<td><strong>theophylline or aminophylline</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Primary options</strong></td>
</tr>
</tbody>
</table>
|         | » **theophylline**: 300 mg/day orally 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 |}
| OR      |                                                                                   |
|         | » **aminophylline**: consult specialist for guidance on dose                      |
|         | » There is no clear recommendation about the exactly appropriate time to use theophylline or aminophylline, but most experts believe in its use when patients have exhausted bronchodilator and corticosteroid options. |
|         | » Toxicity is dose-related.[5][Evidence]                                         |
| adjunct | **long-term oxygen therapy**                                                     |
|         | » 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 oedema suggesting |
congestive cardiac failure, or polycythaemia (haematocrit >55%).[1]

» Oxygen is suggested for patients in whom the predicted PaO2 during air travel is <6.7 kPa (<50 mmHg).[1] 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.[78] [80]

6 Evidence 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

» glycopyrronium/formoterol fumarate inhaled: (14.4/9.6 micrograms/dose inhaler) 1 puff twice daily

OR

» indacaterol/glycopyrronium inhaled: (110/50 micrograms/capsule inhaler) 1 capsule once daily

OR

» 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.[1]

» In addition, a LABA/LAMA combination was superior to a LABA and an inhaled corticosteroid (ICS) combination in preventing exacerbations
### Ongoing

and other patient reported outcomes in group D patients.[1]

- Group D patients are at a higher risk of developing pneumonia when receiving treatment with ICS.[44] [106]

- If a single bronchodilator is chosen as initial treatment, a LAMA is preferred by GOLD guidelines over a LABA.[1]

- 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.[1]

- Patients should not take short-acting anticholinergic agents if they have already been started on tiotropium.[83] [84]

- Umeclidinium/vilanterol, glycopyrronium/formoterol fumarate,[49] indacaterol/glycopyrronium,[53] and tiotropium/olodaterol are combinations of a LABA and a LAMA approved for use in COPD.[48]

<table>
<thead>
<tr>
<th>plus</th>
<th>short-acting bronchodilator as required</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» salbutamol inhaled: (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» ipratropium inhaled: (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required</td>
<td></td>
</tr>
</tbody>
</table>

- Provides symptomatic relief.[7][A]Evidence

- 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.[83] [84]

<table>
<thead>
<tr>
<th>plus</th>
<th>patient education and vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>» Influenza and pneumococcal vaccination should be offered to every COPD patient.[1] 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</td>
<td></td>
</tr>
</tbody>
</table>
COPD Treatment

Ongoing

<table>
<thead>
<tr>
<th>Adjunct</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>of community-acquired pneumonia in patients younger than 65 with an FEV1 of &lt;40%.[102]</td>
<td></td>
</tr>
<tr>
<td>- Patients should be well educated about the disease course and symptoms of exacerbation or decompensation</td>
<td></td>
</tr>
</tbody>
</table>

**Plus** smoking cessation

- 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.[2] Evidence

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

**Plus** pulmonary rehabilitation

- Pulmonary rehabilitation should be started as early as patient group B or C disease.[1]

- 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 dyspnoea, exercise capacity, quality of life, and emotional feelings.[1] [78]

**Adjunct** theophylline or aminophylline

**Primary options**

- **Theophylline**: 300 mg/day orally 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

**OR**

- **Aminophylline**: consult specialist for guidance on dose

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

- Toxicity is dose-related.[5A] Evidence

**Adjunct** long-term oxygen therapy

- Criteria for long-term oxygen therapy include: PaO2 ≤7.3 kPa (55 mmHg); or SaO2 ≤88%, with or without hypercapnia confirmed twice
### Ongoing

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 oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit >55%).[1]

» Oxygen is suggested for patients in whom the predicted PaO₂ during air travel is <6.7 kPa (<50 mmHg).[1] 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.[78] [80]

### Evidence

- **adjunct**
  - **surgical interventions**

  » Criteria for consideration of lung transplantation include patients with a Body-mass index, airflow Obstruction, Dyspnoea, and Exercise (BODE) index of 7 to 10, or at least one of the following: history of hospitalisation for exacerbation associated with acute hypercapnia (PCO₂ >50 mmHg); pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy; FEV₁ <20% and either DLCO <20% or homogeneous distribution of emphysema.[107]

  » Lung volume reduction surgery (LVRS) is indicated in patients with very severe airflow limitation, and especially in patients with localised upper lobe disease and lower than normal exercise capacity. Bullectomy is an option in COPD patients with dyspnoea 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 favourable.

  » Lung transplantation has been shown to improve quality of life and functional capacity.[108] [109] However, lung transplantation does not appear to confer a survival benefit.[110]

- **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.
### Ongoing

before acute respiratory failure develops.[81]

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.[82]

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

#### 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
  
- **AND**

- **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**
  - **glycopyrronium inhaled:** (50 micrograms/capsule inhaler) 50 micrograms (1 capsule) once daily

- In group D patients who develop further exacerbations on LAMA/LABA therapy, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest two alternative pathways: escalation to LAMA/LABA/ICS or switch to LABA/ICS.[1]

- Studies are under way comparing the effects of LABA/LAMA versus LAMA/LABA/ICS for preventing exacerbations.[1]

- If patients treated with LAMA/LABA/ICS (triple therapy) still have exacerbations, additional
### COPD Treatment

| Ongoing | options include adding roflumilast, adding a macrolide antibiotic, and stopping the ICS.[1] 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.[1] |
| plus short-acting bronchodilator as required |
| **Primary options** | |
| » salbutamol inhaled: (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required |
| OR |
| » ipratropium inhaled: (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required |
| » Provides symptomatic relief.[7][A]Evidence |
| » 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.[83] [84] |
| plus patient education and vaccination |
| » Influenza and pneumococcal vaccination should be offered to every COPD patient.[1] 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%. [102] |
| » Patients should be well educated about the disease course and symptoms of exacerbation or decompensation |
| plus smoking cessation |
| » 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.[2][A]Evidence |
| » Nicotine-replacement therapy or other drug therapies, in conjunction with appropriate non-pharmacological therapies, should be used. |
| plus pulmonary rehabilitation |
**Ongoing**

» Pulmonary rehabilitation should be started as early as patient group B or C disease.[1]

» 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 dyspnoea, exercise capacity, quality of life, and emotional feelings.[1] [78]

**adjunct** theophylline or aminophylline

**Primary options**

» **theophylline**: 300 mg/day orally 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

OR

» **aminophylline**: consult specialist for guidance on dose

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

» Toxicity is dose-related.[5][A]Evidence

**adjunct** phosphodiesterase-4 inhibitor

**Primary options**

» **roflumilast**: 500 micrograms orally once daily

» Roflumilast may be considered in patients with an FEV1 <50% predicted and chronic bronchitis,[111] especially if they have experienced at least one hospitalisation for an exacerbation in the previous year.[1] [112]

**adjunct** macrolide antibiotic

**Primary options**

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

OR

» **erythromycin**: 500 mg orally twice daily
Ongoing

» The use of azithromycin is supported by the best available evidence.[113] [114]

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

adjunct long-term oxygen therapy

» 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 oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit >55%).[1]

» Oxygen is suggested for patients in whom the predicted PaO2 during air travel is <6.7 kPa (<50 mmHg).[1] 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.[78] [80] 6[B]Evidence

adjunct surgical interventions

» Criteria for consideration of lung transplantation include patients with a Body-mass index, airflow Obstruction, Dyspnoea, and Exercise (BODE) index of 7 to 10, or at least one of the following: history of hospitalisation for exacerbation associated with acute hypercapnia (PCO2 >50 mmHg); pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy; FEV1 of <20% and either DLCO <20% or homogenous distribution of emphysema.[107]

» Lung volume reduction surgery (LVRS) is indicated in patients with very severe airflow limitation, and especially in patients with localised upper lobe disease and lower than normal exercise capacity. Bullectomy is an option in COPD patients with dyspnoea 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 favourable.

» Lung transplantation has been shown to improve quality of life and functional capacity.[108] [109] However, lung
transplantation does not appear to confer a survival benefit.[110]

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.[81]

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.[82]

2nd 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

» 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 LAMA/LABA/ICS or switch to LABA/ICS.[1]

» Studies are under way comparing the effects of LABA/LAMA versus LAMA/LABA/ICS for preventing exacerbations.[1]

» There is no evidence that switching from LABA/LAMA to LABA/ICS results in better prevention of exacerbations. If LABA/ICS therapy
COPD

Ongoing

does not positively impact exacerbations or symptoms, a LAMA can be added.[1]

» 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.[1]

plus short-acting bronchodilator as required

Primary options

» salbutamol inhaled: (100 micrograms/dose inhaler) 100-200 micrograms (1-2 puffs) every 4-6 hours when required

OR

» ipratropium inhaled: (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to 4 times a day when required

» Provides symptomatic relief.7[A]Evidence

» 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.[83] [84]

plus patient education and vaccination

» Influenza and pneumococcal vaccination should be offered to every COPD patient.[1] 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%.[102]

» Patients should be well educated about the disease course and symptoms of exacerbation or decompensation.

plus smoking cessation

» 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.2[A]Evidence

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

plus pulmonary rehabilitation
Ongoing

» Pulmonary rehabilitation should be started as early as patient group B or C disease.[1]

» 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 dyspnoea, exercise capacity, quality of life, and emotional feelings.[1] [78]

adjunct theophylline or aminophylline

Primary options

» theophylline: 300 mg/day orally 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

OR

» aminophylline: consult specialist for guidance on dose

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

» Toxicity is dose-related.[A]Evidence

adjunct long-term oxygen therapy

» 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 oedema suggesting congestive cardiac failure, or polycythaemia (haematocrit >55%).[1]

» Oxygen is suggested for patients in whom the predicted PaO2 during air travel is <6.7 kPa (<50 mmHg).[1] 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
Ongoing

90% during rest, exercise, and sleep.[78] [80] [6][Evidence]

adjunct surgical interventions

» Criteria for consideration of lung transplantation include patients with a Body-mass index, airflow Obstruction, Dyspnoea, and Exercise (BODE) index of 7 to 10, or at least one of the following: history of hospitalization for exacerbation associated with acute hypercapnia (PCO2 >50 mmHg); pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy; FEV1 of <20% and either DLCO <20% or homogeneous distribution of emphysema.[107]

» Lung volume reduction surgery (LVRS) is indicated in patients with very severe airflow limitation and especially in patients with localised upper lobe disease and lower than normal exercise capacity. Bullectomy is an option in COPD patients with dyspnoea 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 favourable.

» Lung transplantation has been shown to improve quality of life and functional capacity.[108] [108] However, lung transplantation does not appear to confer a survival benefit.[110]

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.[81] 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.[82]
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 tumour necrosis factor antagonists are among these new treatments.[115] 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 proteinase 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.[116] 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.[117] Although retrospective studies showed decreased rate and severity of exacerbations, hospitalisation, and mortality in patients using statin therapy, a prospective study failed to prove this benefit.[118] 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.[119] Palovarotene is a selective retinoic acid receptor gamma agonist that is under investigation for the treatment of emphysema. It is hypothesised that retinoic acid signalling affects alveologenesis. There have been promising results in animal studies.[120] 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 (LAMA/LABA) 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 non-functional 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.[121] [122]

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.[123] [124]
**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 at 6-month intervals, while patients with severe frequent exacerbations, and recently hospitalised 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 dyspnoea 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.[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**

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 optimise 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.

Patients should be encouraged to maintain physical activity.[1]

**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>
</tr>
</tbody>
</table>

Cor pulmonale is right-sided heart failure secondary to long-standing COPD. It is caused by chronic hypoxia and subsequent vasoconstriction in pulmonary vasculature that causes pulmonary hypertension and right-sided heart failure.

Engorged neck veins, a loud P2, lower-extremity oedema, and hepatomegaly are signs of cor pulmonale.

Continuous oxygen therapy is the mainstay of therapy. Judicious use of diuretics is warranted.[133]

| recurrent pneumonia    | variable  | high       |

This PDF of the BMJ Best Practice topic is based on the web version that was last updated: Jun 28, 2018. BMJ Best Practice topics are regularly updated and the most recent version of the topics can be found on bestpractice.bmj.com. Use of this content is subject to our disclaimer. © BMJ Publishing Group Ltd 2018. All rights reserved.
Recurrent pneumonia is a common complication of COPD and a frequent cause of COPD exacerbation. Either viral or bacterial infections can be the cause.

Chronic lung and airway damage, inflammation, compromised ciliary function, and bacterial colonisation 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.[130] [131]

Use of antibiotic therapy has shown some benefit.[132] Usual treatment time is around 7 to 14 days. Appropriate coverage for *Haemophilus influenzae* and *Streptococcus pneumoniae* is mandatory. Pneumococcal vaccination is strongly recommended in COPD patients.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent pneumonia</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>Depression</td>
<td>variable</td>
<td>high</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Anaemia</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Polycythaemia</td>
<td>variable</td>
<td>medium</td>
</tr>
</tbody>
</table>

Depression is a common consequence of COPD. If any mood change occurs, a psychiatric evaluation may be necessary.

Pneumothorax occurs because of lung parenchyma damage with sub-pleural bulla formation and rupture. Spontaneous pneumothorax is very common with chronic severe cough or chest trauma, and may be life-threatening.

High levels of suspicion are necessary for prompt diagnosis. CXR or chest CT confirms the diagnosis.

Conservative management may be sufficient in minor cases. In severe cases, chest tube insertion is necessary to prevent tension pneumothorax and haemodynamic instability. If recurrent pneumothorax occurs, then surgical interventions, such as video-assisted thoracoscopic pleurodesis or bullectomy, are warranted.

A study of a large number of COPD patients with acute respiratory failure reported in-hospital mortality of 17% to 49%. Therapy includes non-invasive positive pressure ventilation and/or mechanical ventilation.

Anaemia is more prevalent than previously thought, affecting almost 25% of COPD patients.[134] A low haematocrit indicates a poor prognosis in COPD patients receiving long-term oxygen treatment.[135]

Secondary polycythaemia can develop in the presence of arterial hypoxaemia, especially in continuing smokers. It can be identified by haematocrit >55%. Many times these patients require supplemental home oxygen.
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. 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 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, and atrial natriuretic peptide 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, dyspnoea, 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 2 factors that improve survival are smoking cessation and oxygen supplementation.
## Diagnostic guidelines

### Europe

**Chronic obstructive pulmonary disease in over 16s: diagnosis and management**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2010

### International

**Global strategy for the diagnosis, management, and prevention of COPD**

*Published by:* Global Initiative for Chronic Obstructive Lung Disease  
*Last published:* 2017

## Treatment guidelines

### Europe

**BTS/ICS guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults**

*Published by:* British Thoracic Society; Intensive Care Society  
*Last published:* 2016

**BTS guideline on pulmonary rehabilitation in adults**

*Published by:* British Thoracic Society  
*Last published:* 2013

**Chronic obstructive pulmonary disease in over 16s: diagnosis and management**

*Published by:* National Institute for Health and Care Excellence  
*Last published:* 2010

### International

**Global strategy for the diagnosis, management, and prevention of COPD**

*Published by:* Global Initiative for Chronic Obstructive Lung Disease  
*Last published:* 2017

### North America

**Nursing care of dyspnea: the 6th vital sign in individuals with chronic obstructive pulmonary disease (COPD)**

*Published by:* Registered Nurses Association of Ontario (Canada)  
*Last published:* 2010
1. Reduction in exacerbations: there is good-quality evidence that a combination of an anticholinergic plus a short-acting beta-2 agonist is more effective than a short-acting beta-2 agonist alone at reducing COPD exacerbations at 12 weeks. This combination does not seem to be more effective at reducing exacerbations compared with an anticholinergic alone.  
   **Evidence level A:** Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

2. Lung function: there is good-quality evidence that smoking cessation interventions are more effective than usual care at improving FEV1 in people with COPD at 1 to 5 years and at reducing all-cause mortality at 14.5 years.  
   **Evidence level A:** Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

3. Reduction in exacerbations: there is good-quality evidence that beta-2 agonists are more effective than placebo at reducing exacerbations at 12 to 52 weeks.  
   **Evidence level A:** Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

4. Lung function: there is medium-quality evidence that ipratropium, a short-acting anticholinergic, is more effective than placebo at improving FEV1 at 12 weeks.  
   **Evidence level B:** Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

5. Lung function: there is good-quality evidence that theophylline is more effective than placebo at increasing FEV1. However, its usefulness is limited by adverse effects and the need for frequent monitoring of blood concentrations.  
   **Evidence level A:** Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

6. Mortality: there is medium-quality evidence that domiciliary oxygen treatment is more effective than no oxygen supplementation at reducing mortality in people with severe daytime hypoxaemia, with continuous oxygen being more effective than nocturnal domiciliary oxygen treatment.  
   **Evidence level B:** Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

7. Lung function: there is good-quality evidence that short-acting beta-2 agonists are more effective than placebo at increasing FEV1 and at improving daily breathlessness scores at 1 week.
**Evidence level A**: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.

8. Reduction in exacerbations: there is good-quality evidence that prophylactic azithromycin reduces the risk of acute exacerbations in patients with stage II, III, or IV COPD. However, when administered for 1 year, the most noted side effect was a decrement in hearing. [114]

**Evidence level A**: Systematic reviews (SRs) or randomized controlled trials (RCTs) of >200 participants.
Key articles


References


<table>
<thead>
<tr>
<th>Reference</th>
<th>Citation</th>
</tr>
</thead>
</table>
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
Disclaimer

This content is meant for medical professionals situated outside of the United States and Canada. The BMJ Publishing Group Ltd (“BMJ Group”) tries to ensure that the information provided is accurate and up-to-date, but we do not warrant that it is nor do our licensors who supply certain content linked to or otherwise accessible from our content. The BMJ Group does not advocate or endorse the use of any drug or therapy contained within nor does it diagnose patients. Medical professionals should use their own professional judgement in using this information and caring for their patients and the information herein should not be considered a substitute for that.

This information is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition such standards and practices in medicine change as new data become available, and you should consult a variety of sources. We strongly recommend that users independently verify specified diagnosis, treatments and follow up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the agent to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region. This information is provided on an “as is” basis and to the fullest extent permitted by law the BMJ Group and its licensors assume no responsibility for any aspect of healthcare administered with the aid of this information or any other use of this information.

View our full Website Terms and Conditions.
Contributors:

// Authors:

Manoochehr Abadian Sharifabad, MD
Fountain Valley Regional Medical Center
Fountain Valley, CA
DISCLOSURES: MAS declares that he has no competing interests.

// Acknowledgements:

Dr Manoochehr Abadian Sharifabad would like to gratefully acknowledge Dr Jonathan P. Parsons and Dr Michael Ezzie, the previous contributors to this monograph. JPP has contributed at speakers' bureaus for GlaxoSmithKline, Inc., Schering-Plough, Inc., and AstraZeneca, Inc. ME declares that he has no competing interests.

// Peer Reviewers:

Hormoz Ashtyani, MD, FCCP
Hackensack University Medical Center
Hackensack, NJ
DISCLOSURES: HA declares that he has no competing interests.

William Janssen, MD
Assistant Professor of Medicine
National Jewish Medical and Research Center, University of Colorado Health Sciences Center, Denver, CO
DISCLOSURES: WJ declares that he has no competing interests.

Francis Thien, MD, FRACP, FCCP
Associate Professor
Director of Respiratory Medicine, Eastern Health & Monash University, Victoria, Australia
DISCLOSURES: FT declares that he has no competing interests.