# Table of Contents

## Overview
- Summary 3
- Definition 3

## Theory
- Epidemiology 4
- Aetiology 4
- Pathophysiology 4
- Case history 5

## Diagnosis
- Approach 7
- History and exam 9
- Risk factors 11
- Investigations 13
- Differentials 18
- Criteria 19
- Screening 20

## Management
- Approach 21
- Treatment algorithm overview 32
- Treatment algorithm 34
- Emerging 67
- Primary prevention 68
- Secondary prevention 68
- Patient discussions 68

## Follow up
- Monitoring 70
- Complications 71
- Prognosis 73

## Guidelines
- Diagnostic guidelines 74
- Treatment guidelines 74

## Online resources 76

## References 77

## Images 98

## Disclaimer 102
Chronic obstructive pulmonary disease (COPD) is a 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.

Diagnostic tests include pulmonary function tests, chest x-ray, chest computed tomography scan, oximetry, and arterial blood gas 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, phosphodiesterase-4 inhibitors, antibiotics, and mucolytics.

Long-term oxygen therapy improves survival in severe COPD.

Pulmonary rehabilitation improves exercise tolerance, dyspnoea, and health status in stable patients.

**Definition**

Chronic obstructive pulmonary disease (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. COPD prevalence is highest in the World Health Organization region of the Americas and lowest in the South-East Asia and Western Pacific regions. The pooled global prevalence is 15.7% in men and 9.93% in women.[7] The prevalence of COPD in the US is estimated at 14%.[8]

Deaths from COPD have increased by 23% since 1990 and COPD is projected to be the third leading cause of death in the world in 2020.[1] [9] [10] This is because of the expanding epidemic of smoking and ageing of the world population and reduced mortality from other causes of death such as cardiovascular disease.[1] [11] Mortality rates in men exceed mortality rates in women.[10]

An international study reported that the prevalence of COPD in never-smokers is 12.2%.[12] This may be due to air pollution or indoor burning of solid fuels in low and middle income countries. In the US, the prevalence of COPD in never-smokers is 2.2%. Many of these cases are attributed to workplace exposures.[13]

**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.[9] Air pollution, indoor burning of biomass fuels, and occupational exposure to dusts, chemical agents, and fumes are other aetiologies. Oxidative stress and an imbalance in proteases and antiproteases are also important factors in the pathogenesis of COPD, especially in patients with alpha-1 antitrypsin deficiency.[1]

**Pathophysiology**

The hallmark of COPD is chronic inflammation that affects central and peripheral airways, lung parenchyma and alveoli, and pulmonary vasculature. Repeated injury and repair leads to structural and physiological changes. The inflammatory and structural changes in the lung increase with disease severity and persist after smoking cessation.[1]

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, alveolar loss, and, finally, vascular bed changes leading to pulmonary hypertension.

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. Oxidative stress and an excess of proteases amplify the effects of chronic inflammation.[1] Airway remodelling thickens the epithelium, lamina propria, smooth muscle, and adventitia of airways less than 2 mm in diameter, leading to progressive loss of patent terminal and transitional bronchioles.[14]

Elastin breakdown and subsequent loss of alveolar integrity causes emphysema.[15] Ciliary dysfunction and increased goblet cell size and number lead to excessive mucus secretion.

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. Hyperinflation and destruction of lung...
Chronic obstructive pulmonary disease (COPD)

**Theory**

Parenchyma predispose patients with COPD 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.[16] [17] Reduced gas transfer may also lead to hypercapnia as the disease progresses.

Systemic inflammatory mediators may contribute to skeletal muscle wasting or cachexia, and initiate or worsen cardiac, metabolic, and skeletal comorbidities.[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 rhinorrhea. She reports a chronic morning cough productive of white sputum, which has increased over the past 2 days. She has had similar episodes each winter for the past 4 years. She has smoked 1 to 2 packs of cigarettes per day for 40 years and continues to smoke. She denies haemoptysis, chills, or weight loss and has not received any relief from over-the-counter cough preparations.

**Other presentations**

Some patients report chest tightness, which often follows exertion and may arise from intercostal muscle contraction. Fatigue, weight loss, muscle loss, and anorexia are common in patients with severe and very severe COPD.[1] Other presentations include weight loss, haemoptysis, cyanosis, and morning headaches secondary to hypercapnia. Chest pain and haemoptysis are uncommon symptoms of COPD and raise the possibility of alternative diagnoses.[2]

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.[3] [4] Patients with COPD often have other comorbidities, including cardiovascular disease,[5] skeletal muscle dysfunction, metabolic syndrome and diabetes, osteoporosis, depression, anxiety, lung cancer, gastro-oesophageal reflux disease, bronchiectasis, obstructive sleep apnoea, and cognitive impairment.[1] A UK study found that 14.5% of patients with COPD had a concomitant diagnosis of asthma.[6]
Chronic obstructive pulmonary disease (COPD)
**Approach**

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

**History**

COPD has an insidious onset and usually presents in older people. A history of productive cough, wheezing, and shortness of breath, particularly with exercise, is typical. Other symptoms include frequent bronchitis, reduced exercise tolerance, waking at night with breathlessness, ankle swelling, and fatigue.[2]

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, comorbidities, and any family history of lung disease should be determined. A history of previous exacerbations and hospitalisations should be sought.

Patients with COPD may also present with acute, severe shortness of breath, fever, and chest pain during acute infectious exacerbation. See our topic on Acute exacerbation of chronic obstructive pulmonary disease for further information.

**Physical examination**

Although rarely diagnostic, a physical examination is an important part of patient care.[1] 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**

Spirometry is the first test for diagnosis of COPD and for monitoring disease progress.[1] [2] [31] It is the most reproducible and objective measure of airflow limitation. Spirometry should be performed after administering an adequate dose of at least one short-acting inhaled bronchodilator to minimise variability.[1] 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.[32] Spirometry also indicates the severity of airflow obstruction. In patients with an FEV1/FVC ratio <0.7:[1]

- FEV1 ≥80% predicted indicates mild COPD
- FEV1 <80% and ≥50% predicted indicates moderate COPD
- FEV1 <50% and ≥30% predicted indicates severe COPD
- FEV1 <30% predicted indicates very severe COPD.

Chest x-ray (CXR) is rarely diagnostic but should be performed 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. These can be found in the GOLD guidelines.[1] GOLD cautions against the use of the mMRC dyspnoea scale alone for assessing patients, as symptoms of COPD go beyond dyspnoea alone. For this reason, the CAT is preferred. However, GOLD acknowledges that the use of the mMRC scale is widespread, and so a threshold of an mMRC grade ≥2 is still included to define “more breathless” patients in its assessment criteria.[1]

The best predictor of frequent exacerbations is a history of previously treated exacerbations.[1] [33] In addition to previous exacerbations, airflow limitation <50% is predictive of exacerbations.[1]

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).

UK guidelines recommend a full blood count (FBC) for all newly diagnosed patients to screen for anaemia or polycythaemia.[2]

**Other tests**

Detailed pulmonary function tests performed in specialist pulmonary function laboratories can measure diffusing capacity of the lung for carbon monoxide (DLCO), flow volume loops, and inspiratory capacity. They are not used routinely but can be helpful in resolving diagnostic uncertainties and for preoperative assessment.[1] Serial peak flow measurements may distinguish COPD from asthma if there is diagnostic uncertainty.[2]

In young patients (<45 years) with a family history or with rapidly progressing disease and lower lobe changes on imaging tests, alpha-1 antitrypsin level should be checked. The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once, especially in areas with high prevalence of alpha-1 antitrypsin deficiency.[34] This may aid in family screening and counselling.

Computed tomography scans show anatomical changes, but their usefulness in diagnosis is confined to patients considered for surgery and for ruling out other pathologies, such as bronchiectasis or lung cancer.[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.[35]

Exercise testing can be useful in patients with a disproportional degree of dyspnoea.[1] [36] It can be performed on a cycle or treadmill ergometer, or by a simple timed walking test (e.g., 6 minutes, or duration <6 minutes).[37] 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.[38]

In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum should be sent for culture.[1] Echocardiogram evaluates suspected cardiac disease or pulmonary hypertension.


### History and exam

#### Key diagnostic factors

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

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

**sputum production (common)**
- Any pattern of chronic sputum production may indicate COPD.

**exposure to risk factors (common)**
- Including exposure to tobacco smoke, air pollution, or indoor solid fuel burning; occupational exposure to dusts, chemicals, vapors, fumes, or gases; genetic factors and developmentally abnormal lung.

#### 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)
- 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.
- 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.

weight loss (uncommon)
- May occur secondary to anorexia.

muscle loss (uncommon)
- Common in patients with severe or very severe COPD.

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

pursed lip breathing (uncommon)
- Involuntary technique to prolong expiration and decrease air trapping.

cyanosis (uncommon)
Chronic obstructive pulmonary disease (COPD)

**Diagnosis**

- 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)**
- COPD itself does not cause clubbing. The presence of clubbing should alert the clinician to a related condition (e.g., lung cancer or bronchiectasis).

**Risk factors**

**Strong**

**Cigarette smoking**
- Most important risk factor.\(^{[10]}\) It causes 40% to 70% of cases of COPD.\(^{[9]}\) Passive exposure to cigarette smoke also increases risk of COPD.
- 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. A systematic review and meta-analysis has shown that the prevalence of COPD in adult offspring of people with COPD is greater than population-based estimates.\(^{[18]}\)

**Weak**

**White ancestry**
- COPD is more common in white people than black and South Asian people, after adjusting for smoking, age, sex, and socioeconomic status.\(^{[19]}\)

**Exposure to air pollution**
- Chronic exposure to dust, traffic exhaust fumes, and sulfur dioxide increases risk of COPD.\(^{[10]}\)

**Exposure to burning solid or biomass fuel**
- Household exposure to burning coal or biomass fuel increases the risk of COPD.\(^{[20]}\)
**occupational exposure to dusts, chemicals, vapors, fumes, or gases**
- Approximately 14% of all cases of COPD are attributable to occupational exposure.[21]

**developmentally abnormal lung**
- Frequent childhood infection may cause scarring of lungs, decrease elasticity, and increase risk for COPD. History of tuberculosis is associated with increased risk COPD.[22]

**male sex**
- COPD is more common in men, likely due to more smokers being male. However, there is a suggestion that women may be more susceptible than men to the effects of tobacco smoke.[23] [24] [25] [26]

**low socio-economic status**
- The risk for developing COPD is increased in people with lower socio-economic status.[27] However, this may reflect exposure to cigarette smoke, pollutants, or other factors.

**rheumatoid arthritis**
- Epidemiological studies indicate an association between risk of COPD and history of rheumatoid arthritis.[22] A meta-analysis showed that compared with controls, patients with rheumatoid arthritis have a significantly increased risk of incident COPD with a pooled relative risk of 1.82.[28]
# Investigations

## 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></td>
<td>mMRC score ranges from 0-4; CAT score ranges from 0-40: mMRC ≥2 or CAT score ≥10 indicates higher symptoms burden</td>
</tr>
<tr>
<td>standardised symptoms score</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>pulse oximetry</td>
<td>low oxygen saturation</td>
</tr>
<tr>
<td></td>
<td>PaCO₂ &gt;50 mmHg and/or PaO₂ of &lt;60 mmHg suggests respiratory insufficiency</td>
</tr>
<tr>
<td>ABG</td>
<td>hyperinflation</td>
</tr>
<tr>
<td>CXR</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>COPD chest x-ray (AP view): hyperinflated lung, flattened diaphragm, increased intercostal spaces</strong></td>
<td><img src="image" alt="COPD chest x-ray (AP view): hyperinflated lung, flattened diaphragm, increased intercostal spaces" /></td>
</tr>
</tbody>
</table>

*From the collection of Manoochehr Abadian Sharifabad, MD*
# Chronic obstructive pulmonary disease (COPD)

## Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COPD chest x-ray (lateral view):</strong> hyperinflated lung, flattened diaphragm, increased antero-posterior diameter (barrel chest) in lateral view.</td>
<td>From the collection of Manoochehr Abadian Shartabad, MD</td>
</tr>
<tr>
<td><strong>FBC</strong></td>
<td>raised haematocrit, anaemia, possible increased WBC count</td>
</tr>
<tr>
<td>• This test may be considered to assess severity of an exacerbation and may show polycythaemia (haematocrit &gt;55%), anaemia, and leucocytosis. UK guidelines advise FBC in all newly diagnosed patients.[2]</td>
<td></td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>signs of right ventricular hypertrophy, arrhythmia, ischaemia</td>
</tr>
<tr>
<td>• Risk factors for COPD are similar to those for ischaemic heart disease, so comorbidity is common. Right-sided heart failure may develop in longstanding COPD (cor pulmonale).</td>
<td></td>
</tr>
</tbody>
</table>
### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pulmonary function tests</strong></td>
<td>obstructive pattern, decreased DLCO</td>
</tr>
<tr>
<td>• Useful for resolving diagnostic uncertainties and preoperative assessment. Requires specialist laboratory facilities.</td>
<td></td>
</tr>
<tr>
<td>• Decreased diffusing capacity of the lung for carbon monoxide (DLCO) is supportive of emphysema over chronic bronchitis.</td>
<td></td>
</tr>
<tr>
<td><strong>chest CT scan</strong></td>
<td>hyperinflation</td>
</tr>
<tr>
<td>• Provides better visualisation of type and distribution of lung tissue damage and bulla formation than CXR.</td>
<td></td>
</tr>
<tr>
<td><strong>serial peak flow measurement</strong></td>
<td>&lt;20% diurnal or day-to-day variability</td>
</tr>
<tr>
<td>• May be used to exclude asthma if there is diagnostic uncertainty.</td>
<td></td>
</tr>
<tr>
<td><strong>sputum culture</strong></td>
<td>infecting organism</td>
</tr>
<tr>
<td>• In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum should be sent for culture.</td>
<td></td>
</tr>
<tr>
<td><strong>alpha-1 antitrypsin level</strong></td>
<td>should be normal in patients with COPD</td>
</tr>
<tr>
<td>• Low level in patients with alpha-1 antitrypsin deficiency. Test is done if there is high suspicion for alpha-1 antitrypsin deficiency, such as a positive family history and atypical COPD cases (young patients and non-smokers). The World Health Organization recommends that all patients with a diagnosis of COPD should be screened.</td>
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</tr>
<tr>
<td>Test</td>
<td>Result</td>
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<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Once, especially in areas with high prevalence of alpha-1 antitrypsin deficiency.[34]</td>
<td>Poor exercise performance or exertional hypoxaemia is suggestive of advanced disease</td>
</tr>
<tr>
<td><strong>Exercise testing</strong></td>
<td></td>
</tr>
<tr>
<td>• Can be of value in patients with a disproportional degree of dyspnoea compared with spirometry.[36]</td>
<td>Elevated apnoea-hypopnoea index and/or nocturnal hypoxaemia</td>
</tr>
<tr>
<td>It can be performed on a cycle or treadmill ergometer, or by a simple timed walking test (e.g., 6 minutes, or duration &lt;6 minutes).[37]</td>
<td></td>
</tr>
<tr>
<td>Exercise testing is of use in selecting patients for rehabilitation.</td>
<td></td>
</tr>
<tr>
<td><strong>Sleep study</strong></td>
<td></td>
</tr>
<tr>
<td>• Obstructive sleep apnoea, a common finding in patients with COPD, is associated with increased risk of death and hospitalisation in patients with COPD.[35]</td>
<td>Reduced maximal inspiratory pressure</td>
</tr>
<tr>
<td><strong>Respiratory muscle function</strong></td>
<td></td>
</tr>
<tr>
<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.[38]</td>
<td>May be normal or may show right sided heart failure and/or pulmonary hypertension</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td></td>
</tr>
<tr>
<td>• To assess cardiac status if cardiac disease or pulmonary hypertension are suspected.[2]</td>
<td></td>
</tr>
</tbody>
</table>
# Differentials

<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 history of allergy, rhinitis, and eczema is often present. There is daily variability in symptoms, and patients have overt wheezing that usually rapidly responds to bronchodilators. Cough variant asthma mimics many features of COPD.</td>
<td>• Spirometry shows reversibility with bronchodilators. Pulmonary function tests 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 chest x-ray 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 chest x-ray 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>• Pulmonary function tests in bronchiolitis can present with obstructive, restrictive, or mixed pattern. Chest x-ray 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>
</tbody>
</table>
### Condition | Differentiating signs / symptoms | Differentiating tests
--- | --- | ---
**Upper airway dysfunction** | • 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. | • 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.

**Chronic sinusitis/ postnasal drip** | • Chronic sinusitis/rhinitis is a very common cause of chronic cough. Patients may complain of sinus pressure, rhinorrhoea, non-productive cough, and/or headache. | • Nasal endoscopy, CT of sinuses and/or empirical trial of antihistamines is commonly utilised to aid in diagnosis.

**Gastro-oesophageal reflux disease (GORD)** | • Patients with GORD often have dyspepsia and frequent belching, and can have a chronic cough that worsens at night when supine. | • Diagnosis is usually based on response to empirical therapy with proton-pump inhibitors.

**ACE inhibitor-induced chronic cough** | • ACE inhibitors can cause chronic cough; however, the cough is usually non-productive. | • Diagnosis is usually based on improvement of symptoms after empirical cessation of ACE inhibitor.

**Lung cancer** | • Patients may have weight loss, night sweats, haemoptysis, and/or chest or back pain. • People with COPD are also at increased risk of lung cancer. | • Radiography is important in the assessment for lung cancer. Bronchoscopy may be necessary to evaluate for endobronchial cancer if suspicion is high.

### 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. These can be found in the GOLD guidelines.[1] GOLD cautions against the use of the mMRC dyspnoea scale alone for assessing patients, as symptoms of COPD go beyond dyspnoea alone. For this reason, the CAT is preferred. However, GOLD acknowledges that the use of the mMRC scale is widespread, and so a threshold of an mMRC grade ≥2 is still included to define “more breathless” patients in its assessment criteria.[1]

• Group A: low risk (0-1 exacerbation per year, not requiring 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).

Screening

There are no data to show conclusively that screening spirometry is effective in directing management decisions or in improving COPD outcomes in asymptomatic patients.[39] However, if COPD is diagnosed at an early stage and risk factors are eliminated, the rate of decline in lung function will dramatically decrease.[40]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines advocate active case-finding by performing spirometry in patients with symptoms and/or risk factors for COPD.[1] UK guidelines advise spirometry in all patients aged 35 years or older who are current or former smokers and have a chronic cough, to detect cases at an early stage. Clinicians should also consider conducting screening spirometry in all patients with findings compatible with emphysema on chest x-ray or computed tomography of the chest.[2] Significant pulmonary dysfunction may be present in asymptomatic smokers.
Approach

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

The ultimate goals of treatment of COPD are to prevent and control symptoms, to reduce the severity and number of exacerbations, to improve respiratory capacity for increased exercise tolerance, and to reduce mortality.[1]

There is a stepwise approach to therapy and 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.

The World Health Organization (WHO) has specified a minimum set of interventions for the management of stable COPD in primary care. [WHO: package of essential noncommunicable (PEN) disease interventions for primary health care](https://www.who.int/publications/i/item/who-package-of-essential-noncommunicable-(pen)-disease-interventions-for-primary-health-care)

### 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.[41] Such assessment of the medical history should include:

**Exposure to risk factors and preventative measures:**

- Tobacco smoke
- Indoor and outdoor air pollution
- 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**
Chronic obstructive pulmonary disease (COPD) Management

- 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) which may add to symptoms and impact prognosis.

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.) work together with patients, has been shown to improve quality of life and decrease hospital admissions.[42]

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. See our topic on Acute exacerbation of chronic obstructive pulmonary disease for further information.

Chronic management: stepwise therapy according to GOLD group

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that initial treatment is determined by the patient’s GOLD group at diagnosis:[1]

- Rescue short-acting bronchodilators should be prescribed to all patients for immediate symptom relief. Failure to respond to short-acting bronchodilator may signify an acute exacerbation.
- For group A patients (few symptoms and low risk of exacerbations), a short-acting or a long-acting bronchodilator is offered first-line. Long-acting beta-2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are preferred over short-acting bronchodilators, except for patients with only occasional dyspnoea.[1] LABAs and LAMAs both significantly improve lung function, dyspnoea, and health status and reduce exacerbation rates. LAMAs have a greater effect on exacerbation reduction than LABAs.[1] [43] [44] The effect of the bronchodilator should be evaluated. It should be continued if effective, otherwise it should be stopped and another class of bronchodilator or another inhaler device should be tried.[1]
- For group B patients (more symptoms and low risk of exacerbations), a long-acting bronchodilator should be offered first-line. Either a LAMA or a LABA may be prescribed. There is no evidence to recommend one class of long-acting bronchodilator over another for initial treatment in this group of patients. The choice should depend on the patient's perception of symptom relief. For patients with severe breathlessness, initial treatment with two bronchodilators of different classes may be warranted.
- For group C patients (few symptoms but higher risk of exacerbations), first-line treatment should be a LAMA, as LAMAs have a greater effect on exacerbation reduction than LABAs in patients with moderate to very severe COPD.[1] [44] [45]
- For group D patients (more symptoms and high risk of exacerbations), GOLD recommends starting therapy with a LAMA, a LABA/LAMA combination, or an inhaled corticosteroid (ICS)/LABA combination. A LAMA is the first choice for most patients. A LABA/LAMA combination should be considered if the patient is highly symptomatic (COPD assessment test [CAT] score >20),
Chronic obstructive pulmonary disease (COPD)

Management especially if the patient has significant dyspnoea and/or exercise limitation, and an ICS/LABA combination should be considered if the patient’s blood eosinophil count is ≥300 cells/microlitre or the patient has a history of asthma. ICS increases the risk of developing pneumonia in some patients, so should only be used as initial therapy after the possible clinical risks and benefits have been evaluated.

Further treatment is determined by the patient’s dyspnoea/exercise limitation symptom burden and frequency of exacerbations after review and is independent of the patient’s GOLD group at diagnosis.[1] GOLD recommends different treatment pathways depending on whether the primary treatment goal is relieving dyspnoea/exercise limitation symptoms or reducing exacerbations. If treatment is required for both purposes, clinicians should follow the exacerbation pathway. Patients should be reviewed for symptoms and exacerbation risk, and their inhaler technique and treatment adherence assessed, prior to any adjustment in treatment.[1] The role of non-pharmacological treatment should also be assessed. Adjustment of pharmacological treatment can consist of escalation or de-escalation of therapy, as well as switching inhaler devices or molecules within the same drug class. If treatment is changed, then clinicians should review the patient for a clinical response, and for any potential side effects.[1]

Recommended escalation therapy for patients with persistent dyspnoea/exercise limitation after initial therapy is as follows:[1]

- Patients taking long-acting bronchodilator monotherapy should start a second long-acting bronchodilator from a different class. If symptoms do not improve, the second long-acting bronchodilator should be stopped. Changing inhaler device or molecules may be considered.
- For patients taking LABA/ICS therapy, LAMA may be added (triple therapy). Alternatively, LABA/ICS may be switched to LABA/LAMA if the original indication for LABA/ICS was not appropriate, if the patient has not responded to ICS treatment, or if there are significant ICS adverse effects.
- Dyspnoea due to other causes should be considered, investigated, and treated. Inhaler technique and adherence should also be re-assessed, as these may have led to an inadequate response to treatment.

Recommended escalation therapy for patients with persistent exacerbations after initial therapy is as follows:[1]

- Patients taking long-acting bronchodilator monotherapy should increase therapy to either LABA/LAMA or LABA/ICS. Blood eosinophil counts can identify patients who are more likely to respond to ICS.[46] LABA/ICS may be considered in patients with two or more moderate exacerbations per year, or at least one severe exacerbation needing hospital admission in the previous year, and an eosinophil count ≥100 cells/microlitre, or if the history/clinical findings are suggestive of asthma.[1] Patients who have one exacerbation per year are more likely to respond to LABA/ICS if their peripheral eosinophil count is ≥300 cells/microlitre.[47] Patients who take a LABA or LAMA who have blood eosinophils <100 cells/microlitre or who have contraindications to ICS should commence a LABA/LAMA.
- Patients who take LABA/LAMA and whose blood eosinophils are ≥100 cells/microlitre should escalate to triple therapy with LABA/LAMA/ICS. Multiple studies support triple therapy with LABA/LAMA/ICS as being superior to single- or double-agent therapy with LABA/LAMA or LABA/ICS regarding rate of moderate to severe COPD exacerbations and rate of hospitalisation.[48] [49] [50] [51] [52] [53] [54] [55] [56] American Thoracic Society guidelines recommend the use of triple therapy in patients who have had one or more exacerbations requiring oral corticosteroids, antibiotics, or hospitalisation in the past year and who have symptoms of dyspnoea or reduced
exercise tolerance despite LABA/LAMA dual therapy.[57] UK guidelines recommend the use of triple therapy in patients who have an exacerbation requiring hospitalisation, or two moderate exacerbations within a year, despite dual therapy with LABA/LAMA.[2]

- Patients who take a LABA/LAMA and whose blood eosinophils are <100 cells/microlitre should add roflumilast or azithromycin.
- Patients who take LABA/ICS should escalate to triple therapy by adding a LAMA. If ICS is ineffective or causing significant adverse effects, patients may switch to LABA/LAMA.
- Patients who take LABA/LAMA/ICS may add roflumilast or azithromycin. Roflumilast may be considered in patients with forced expiratory volume in 1 second (FEV1) <50% predicted and chronic bronchitis, particularly if they have had at least one hospitalisation for an exacerbation in the last year. The risk of developing antibiotic-resistant organisms should be considered when prescribing azithromycin. ICS can be discontinued if it is ineffective or causing adverse effects. Patients with blood eosinophils ≥300 cells/microlitre are at greatest risk of exacerbations after withdrawing ICS.[58]

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

**Bronchodilators**

Beta-2 agonists are widely used in the treatment of COPD. They increase intracellular cAMP, leading to respiratory smooth muscle relaxation and reduced airway resistance. Muscarinic antagonists (anticholinergics) act as bronchodilators by blocking the cholinergic receptors on the respiratory smooth muscle. This causes muscle relaxation and reduces airflow limitation. Beta agonists and muscarinic antagonists, therefore, provide bronchodilator effects through different pathways. Both are available as short-acting and long-acting preparations.

Short-acting beta-2 agonists (e.g., salbutamol) and short-acting muscarinic antagonists (e.g., ipratropium) improve lung function and breathlessness and quality of life. Ipratropium may have a small benefit over short-acting beta-2 agonists in improving health-related quality of life.[59] These agents can be used as rescue therapy when the patient is using long-acting bronchodilator therapy and may be used as initial treatment for patients in GOLD group A if patients only have occasional dyspnoea.[1] [60] However, regular use of short-acting bronchodilators is not generally recommended.

Tiotropium, a LAMA, has been shown to reduce risk of exacerbation versus placebo or other maintenance treatments.[61] Newer LAMAs, such as aclidinium, glycopyrronium, and umeclidinium, have at least comparable efficacy to tiotropium, in terms of change from baseline in trough FEV1, transitional dyspnoea index focal score, St George's Respiratory Questionnaire score, and rescue medication use.[62] Revefenacin is a nebulised LAMA approved for the maintenance treatment of moderate to severe COPD. There is a suggestion of increased cardiovascular-related mortality in some studies of patients taking short-acting muscarinic antagonists and in some studies of patients taking LAMAs.[63] [64] One study concluded that aclidinium was not associated with an increase in major adverse cardiovascular events, compared with placebo.[65] A population-based cohort study found that older men with COPD newly started on LAMAs are at increased risk of urinary tract infections.[66]

LABAs and LAMAs both significantly improve lung function, dyspnoea, and health status and reduce exacerbation rates. In cases of stable COPD, if the decision is made to use single-agent therapy, LAMA may be superior to LABA agents.[67] LAMAs have a greater effect on exacerbation reduction than LABAs in patients with moderate to very severe COPD.[1] [43] [44] The long-term safety of LAMA was demonstrated in the UPLIFT trial.[68]
A LABA/LAMA combination may provide a better therapeutic effect without increasing the adverse effects of each class. Combination therapy with a LABA/LAMA reduces exacerbation rate compared with monotherapy. Once-daily LABA/LAMA delivered via a combination inhaler is more associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild/moderate COPD, compared with placebo. Compared to LABA/ICS, a LABA/LAMA combination has fewer exacerbations, a larger improvement of FEV1, a lower risk of pneumonia, and more frequent improvement in quality of life. A systematic review and network meta-analysis found that all LABA/LAMA fixed-dose combinations had a similar efficacy and safety.

Umeclidinium/vilanterol, glycopyrronium/formoterol, indacaterol/glycopyrronium, tiotropium/olodaterol, and aclidinium/formoterol are LABA/LAMA combinations approved for use in COPD. Indacaterol/glycopyrronium showed superior efficacy compared with glycopyrronium or tiotropium in patients with moderate to severe COPD, and compared with salmeterol/fluticasone in preventing COPD exacerbation. Umeclidinium/vilanterol decreases the risk of exacerbations in patients with mild/moderate COPD.

As outlined above, GOLD makes recommendations on the initial agent based on the patient’s risk group (A, B, C, or D). American Thoracic Society guidelines recommend initiating LABA/LAMA dual therapy in preference to monotherapy in patients with COPD who have dyspnoea or exercise intolerance. UK guidelines recommend initiating dual therapy with a LABA/LAMA or LABA/ICS if a patient has symptoms or exacerbations despite non-pharmacological treatment and using a short-acting bronchodilator as needed. The choice of initial drug regimen in the UK guidance is based on whether or not the patient has features of asthma or features suggesting corticosteroid responsiveness.

Inhaled corticosteroids

Inhaled corticosteroids are indicated in some patients with COPD who suffer from frequent exacerbations. They should always be prescribed in combination with long-acting bronchodilators. 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. Blood eosinophil count may predict the effectiveness of adding inhaled corticosteroids to regular long-acting bronchodilator treatment to prevent exacerbations. Little or no effect is seen at blood eosinophil counts of <100 cells/microlitre, while maximal effect is seen at blood eosinophil counts of >300 cells/microlitre. These thresholds indicate approximate cut-off values which may help clinicians predict the likelihood of a treatment benefit. Former smokers are more corticosteroid-responsive than current smokers at any eosinophil count. Both current and former smokers with COPD can benefit from ICS in terms of lung function and rates of exacerbations, although the effect is smaller for heavy or current smokers compared with light or former smokers.

Several studies have pointed to an increased risk of pneumonia in patients with COPD taking inhaled corticosteroids. This risk is slightly higher for fluticasone in comparison with budesonide. A systematic review and meta-analysis found that, despite a significant increase in unadjusted risk of pneumonia associated with use of inhaled corticosteroids, pneumonia mortality and overall mortality were not increased in randomised controlled trials and were decreased in observational studies. Therefore, an individualised treatment approach that assesses a patient's risk of pneumonia versus the benefit of
Chronic obstructive pulmonary disease (COPD) Management

decreased exacerbations should be implemented. Concern is also raised with regards to increased risk of tuberculosis and influenza in adult patients with COPD who are on inhaled corticosteroid therapy. ICS may also cause oropharyngeal candidiasis and hoarseness.

Clinicians should weigh the potential benefits and risks of prescribing ICS and discuss these with the patient. A history of hospitalisation(s) for exacerbations of COPD, two or more moderate exacerbations per year despite regular long-acting bronchodilators, blood eosinophils of ≥300 cells/microlitre, and/or previous or concomitant asthma all strongly favour initiating ICS. Repeated episodes of pneumonia, blood eosinophils <100 cells/microlitre, and/or history of mycobacterial infection are all factors against the use of ICS. Use of ICS can be considered in patients with one moderate exacerbation of COPD per year despite regular long-acting bronchodilator therapy and/or peripheral eosinophils 100-300 cells/microlitre.

Long-term use of oral corticosteroids in COPD is not recommended. Some patients with severe disease are unable to completely stop treatment after starting oral corticosteroids for an acute exacerbation. In this case, the dose should be kept as low as possible and consideration given to osteoporosis prophylaxis.

Combined bronchodilator and corticosteroid preparations

A combination preparation of a long-acting bronchodilator and an 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 an inhaled corticosteroid and a LABA is superior to use of either agent alone. The combination may be provided in separate inhalers or a combination inhaler.

Multiple studies support triple therapy with LABA/LAMA/ICS as being superior to single- or double-agent therapy with LABA/LAMA or LABA/ICS regarding rate of moderate to severe COPD exacerbations and rate of hospitalisation. Use of ICS also slows the rate of decline in lung function following an exacerbation in patients with mild to moderate COPD and elevated blood eosinophils. One randomised controlled trial has reported a reduction in all-cause mortality in patients with FEV1 <50% and at least one exacerbation in the past year who take fluticasone furoate/umeclidinium/vilanterol, compared with patients taking umeclidinium/vilanterol. Patients with mild COPD and at least two moderate or one severe exacerbations in the last year also had reduced all-cause mortality when taking fluticasone furoate/umeclidinium/vilanterol, compared with umeclidinium/vilanterol. Another randomised controlled trial had similar findings in terms of mortality in the triple therapy arm (budesonide/glycopyrronium/formoterol), but only at the higher dose of ICS. The same study showed that increasing the dose of budesonide in triple therapy does not decrease the rate of exacerbations, compared with standard dose triple therapy. For both studies, there were no differences in mortality compared with LABA/ICS. A post hoc pooled analysis of three trials of triple therapy in patients with COPD and severe airflow limitation and a history of exacerbations showed a non-significant trend for lower mortality with triple therapy compared with non-ICS treatments.

Before prescribing triple therapy, clinicians should assess whether another physical or mental condition could be causing the patient’s symptoms. UK guidelines advise clinicians to review patients taking triple therapy for relief of daily symptoms after 3 months. Treatment should be changed to LABA/LAMA if the patient’s symptoms have not improved. The ICS may be withdrawn if the patient has had no exacerbations in the past year.
Phosphodiesterase-4 inhibitors

Roflumilast is an oral phosphodiesterase-4 inhibitor which inhibits the breakdown of cAMP. It may be considered in patients with FEV1 <50% predicted and chronic bronchitis who are taking LABA/LAMA/ICS, particularly if they have had at least one hospitalisation for an exacerbation in the last year.[1] Roflumilast offers benefit in improving lung function and reducing the likelihood of exacerbations. However, it has little impact on quality of life or symptoms.[98]

Antibiotics

Prophylactic antibiotics, such as macrolides, may be considered for reducing the risk of acute exacerbation, particularly in patients who have frequent exacerbations and are refractory to standard therapy.[99] [100] [101] Use of prophylactic macrolide antibiotics decreases the frequency of exacerbations in patients with COPD but long-term azithromycin use is associated with clinically significant hearing loss, which in many cases was reversible.[102] There are no data showing the efficacy or safety of chronic azithromycin treatment beyond 1 year of treatment.

Azithromycin therapy is believed to be most effective in preventing acute exacerbation, with greater efficacy seen in older patients and milder GOLD stages. Little evidence of treatment benefit is seen in current smokers.[103] Azithromycin increases the risk of colonisation with macrolide-resistant organisms and should not be prescribed for patients with hearing impairment, resting tachycardia, or apparent risk of QTc prolongation.[104]

UK guidelines advise that prophylactic azithromycin could be considered for patients who have more than three acute exacerbations requiring corticosteroid therapy and at least one exacerbation requiring hospitalisation per year.[105] Before starting prophylactic antibiotics, baseline ECG and liver function tests should be performed, a sputum sample obtained for culture and sensitivity (including tuberculosis testing), the patient’s sputum clearance technique should be optimised, and bronchiectasis should be excluding with a CT scan.[2] [105] ECG and liver tests should be repeated after 1 month of treatment. A head-to-head comparison of fluoroquinolones, tetracyclines, and macrolides given for 12 to 13 weeks to people with COPD did not identify a difference in efficacy or safety between antibiotic classes, but the sample sizes of included studies were small and the studies were of short duration; further research is required in this area.[106]

Prophylactic antibiotic therapy should be reviewed at 6 and 12 months to determine whether there is a benefit in terms of exacerbation rates.[105] If antibiotic therapy is not effective it should be stopped.

Methylxanthines

Theophylline (a methylxanthine agent) is a bronchodilator that acts by increasing cAMP and subsequent respiratory smooth muscle relaxation. It is not commonly used because of limited potency, narrow therapeutic window, high risk profile, and frequent drug-drug interactions. Theophylline is indicated for persistent symptoms if inhaled therapy is insufficient to relieve airflow obstruction. Theophylline has modest effects on lung function in moderate to severe COPD.[107] GOLD advise that theophylline should only be used if other long-term bronchodilator treatments are unavailable or unaffordable.[1] Experts may prescribe theophylline after a patient has exhausted all options for inhaled therapies.

Patient education and self-management

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

One Cochrane review found that self-management interventions that include an action plan for acute exacerbations of COPD are associated with improvements in health-related quality of life and fewer admissions to hospital for respiratory problems. An exploratory analysis found a small, but significantly higher, respiratory-related mortality rate for self-management compared to usual care, although no excess risk of all-cause mortality was seen.[108] A randomised controlled trial showed that a 3-month programme of self-management started in patients with COPD exacerbations recently discharged from hospital led to increases in COPD-related hospitalisations and emergency department visits over 6 months.[109]

Self-management plans should include personalised advice on: breathlessness and stress management techniques, energy conservation, avoiding aggravating factors, how to monitor symptoms, how to manage worsening symptoms, and contact information to use in the event of an exacerbation.[1]

Helping patients to self-manage should ideally address psychosocial concerns and patients' personal beliefs about COPD and its management. Many patients report losses and limitations on their lifestyle and social interaction after a diagnosis of COPD. Symptoms of anxiety, depression, and frustration are common.[110] A systematic review found a small beneficial effect of cognitive behavioural therapy-based psychological treatment and symptoms of depression, compared with education or no intervention, although the evidence was limited by heterogeneity between trials and inability to blind participants and researchers to the intervention.[111]

One randomised controlled trial found that a telephone health coaching intervention to promote behaviour change in patients with mild COPD in primary care led to improvements in self-management activities, but did not improve health-related quality of life.[112] A meta-analysis found that health coaching that included goal setting, motivational interviewing, and COPD-related health education significantly improved health-related quality of life and reduced hospital admissions for an exacerbation of COPD, but did not decrease all-cause hospital admissions.[113]

Patients who use inhaled therapies should receive training on inhaler device technique. The majority of patients make at least one error in using their inhaler and incorrect inhaler use is associated with worse disease control.[114][115] Poor technique is more likely when patients are using multiple devices or have never received inhaler technique training.[116] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[117] Demonstration using a placebo device may be most effective for teaching inhaler technique to adults aged ≥65 years.[118] Patients should be asked to bring their inhalers to clinic to facilitate a review of inhaler use.[1] Pharmacist-led interventions and lay health coaching can improve inhaler technique and adherence in patients with COPD.[119] [120]

Physical activity is recommended for all patients with COPD.[1] One systematic review and meta-analysis of randomised controlled trials found that exercise training on its own can improve physical activity in COPD, and greater improvements can be made with the addition of physical activity counselling.[121] Another systematic review and meta-analysis found that a combination of aerobic exercise and strength training was more effective than strength training or endurance training alone in increasing the 6-minute walking distance.[122] A Cochrane review found limited evidence for improvement in physical activity with physical activity counselling, exercise training, and pharmacological management of COPD. The authors commented that assessment of quality had been limited by lack of methodological detail and the diverse range of interventions had primarily been assessed in single studies.[123] The optimal timing,
components, duration, and models for improving physical activity remain unclear. Meta-analyses suggest that yoga and Qigong can improve exercise capacity and pulmonary function in patients with COPD.[124][125]

**Smoking cessation and vaccination**

Smoking cessation should be encouraged in all patients, in addition to guidance on avoiding exposure to occupational or environmental tobacco smoke and other irritants.[1][2] Smoking cessation significantly reduces the rate of progression of COPD and risk of malignancies. It also reduces the risk of coronary and cerebrovascular diseases. Among different therapeutic modalities in COPD, the only two factors that improve survival are smoking cessation and oxygen supplementation.

Usual smoking-cessation programmes include counselling, group meetings, and drug therapy.[126] Some patients may need frequent referrals to achieve success. 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.[127][128][129] The effectiveness and safety of e-cigarettes/vaping as an aid to smoking cessation is uncertain.[1]

Patients should be vaccinated against influenza virus and *Streptococcus pneumoniae.*[1][130] Vaccination against influenza is associated with fewer exacerbations of COPD.[130][131] Guidance from the US Centers for Disease Control and Prevention (CDC) advises a single dose of pneumococcal 23-valent polysaccharide vaccine (PPSV23) for all patients with COPD who have not previously received the recommended pneumococcal vaccine.[132] The CDC recommends shared decision-making regarding administration of the PCV13 (pneumococcal 13-valent conjugate vaccine) to people aged 65 years and older who do not have an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant, and who have not previously received PCV13. If a decision to give PCV13 is made, PCV13 should be given first, followed by PPSV23 at least 1 year later.[133]

The CDC also recommends the tetanus/diphtheria/pertussis vaccine in people with COPD who were not vaccinated in adolescence.[134]

**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 and in days of disability per month, but do not improve lung function or quality of life.[135] One meta-analysis comparing erdosteine, carbocisteine, and acetylcysteine concluded that erdosteine had the most favourable safety and efficacy profile. Erdosteine reduced the risk of hospitalisation due to an acute exacerbation, and erdosteine and acetylcysteine reduced the duration of an acute exacerbation.[136] Erdosteine and carbocisteine are not available in the US and some other countries. Treatment with mucolytic agents such as carbocisteine and acetylcysteine may be most beneficial for patients not on inhaled corticosteroids.[1] However, erdosteine may have a significant effect on mild exacerbations whether or not the patient is taking inhaled corticosteroids.[1]

**Pulmonary rehabilitation**

Pulmonary rehabilitation compromises aerobic exercise, strength training, and education. It 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. GOLD guidelines recommend pulmonary rehabilitation for patient groups B to D.[1]

Pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.[137] Extensive pulmonary rehabilitation following hospital admission with an acute exacerbation of COPD decreases the risk of readmission, improves health-related quality of life, and reduces mortality. It also decreases the depression and anxiety related to this disease, and reduces hospitalisation in patients with COPD.[138] The benefit appears to subside after termination of the course unless patients follow a home exercise schedule.[139] Benefits of home- or community-based pulmonary rehabilitation on respiratory symptoms and quality of life in patients with COPD could match those of the hospital-based rehabilitation programmes.[140] [141] 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.[142] There is evidence to support starting pulmonary rehabilitation within 1 month of an acute exacerbation.[143] [144]

Oxygen therapy and ventilatory support

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

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

Guidelines from the American Thoracic Society (ATS) recommend prescribing long-term oxygen therapy for at least 15 hours per day in adults with COPD who have severe chronic resting room air hypoxaemia. The ATS defines severe hypoxaemia as either:[145]

- $\text{PaO}_2 \leq 7.3 \text{kPa (55 mmHg)}$ or oxygen saturation as measured by pulse oximetry ($\text{SpO}_2$) $\leq 88\%$; or
- $\text{PaO}_2$ 7.5-7.9 kPa (56-59 mmHg) or $\text{SpO}_2$ of 89% plus one of the following: oedema, haematocrit $\geq 55\%$, or $P$ pulmonale on an ECG.

For patients prescribed home oxygen therapy, the ATS recommends that the patient and their caregivers should receive instruction and training on the use and maintenance of all oxygen equipment and education on oxygen safety, including smoking cessation, fire prevention, and tripping hazards.[145]

Supplemental oxygen should be titrated to achieve $\text{SaO}_2 \geq 90\%$. [1] The patient should be reassessed after 60 to 90 days to determine whether oxygen is still indicated and is therapeutic.[1] Among different therapeutic modalities in COPD, the only two factors that improve survival are smoking cessation and oxygen supplementation.

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] [31]

There is some evidence that oxygen can relieve breathlessness when given during exercise to mildly hypoxaemic and non-hypoxaemic people with COPD who do not otherwise qualify for home oxygen therapy.[146] The ATS suggests prescribing ambulatory oxygen (oxygen delivered during exercise or activities of daily living) in adults with COPD who have severe exertional room air hypoxaemia.[145]
However, the ATS suggests not prescribing long-term oxygen therapy in adults with COPD who have moderate chronic resting room air hypoxaemia (SpO₂ of 89%-93%).[145]

Air travel is safe for most patients receiving long-term oxygen therapy.[1] Patients with SaO₂ >95% at sea level and SaO₂ ≥84% after a 6-minute walk test may travel by air without further assessment.[1][147] Supplemental oxygen is recommended for patients with SaO₂ 92% to 95% at sea level and SaO₂ <84% after a 6-minute walk test, and for patients with SaO₂ <92% at sea level.[147] Hypoxia-altitude simulation testing should be performed for other patients.[147]

For patients who have COPD and obstructive sleep apnoea, ventilatory support with continuous positive airway pressure (CPAP) can improve survival and reduce hospital admissions.[1][148] Non-invasive ventilation is occasionally used in patients with very severe but stable COPD, although the best selection criteria for candidates is unclear.[1][149]

### Surgery

Surgical interventions (bullectomy, lung volume reduction surgery,[150][151] 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.[151] Lung volume reduction surgery is indicated in patients with very severe airflow limitation, and especially in patients with localised upper lobe disease and lower than normal exercise capacity.[150] 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. Endobronchial valve insertion can produce clinically meaningful improvements in appropriately selected patients with COPD.[152]

### Criteria for referral for lung transplantation include:[153]

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

Lung transplantation has been shown to improve quality of life and functional capacity.[151] However, lung transplantation does not appear to confer a survival benefit.[154]

### Palliative care

Palliative therapies to improve symptoms of dyspnoea, offer nutritional support, address anxiety and depression, and reduce fatigue may benefit patients with COPD who experience these despite optimal medical therapy.[1] End-of-life care and hospice admission should be considered for patients with very advanced disease. 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.[155] Opioid analgesics, fans, neuromuscular electrical stimulation, and chest wall vibration can relieve dyspnoea.[1] Long-acting oral and parenteral opioids may be considered for treating dyspnoea in patients with severe COPD.[1] 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.[156]
Chronic obstructive pulmonary disease (COPD)

Management

One Cochrane review concluded that there is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD.[157]

Acupuncture and acupressure may also improve breathlessness and quality of life in patients with advanced COPD.[158]

**Treatment algorithm overview**

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

<table>
<thead>
<tr>
<th>Acute</th>
<th>1st</th>
<th>2nd</th>
<th>( summary )</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD group A: initial treatment</td>
<td>short- or long-acting bronchodilator</td>
<td>plus</td>
<td>supportive care and advice</td>
</tr>
<tr>
<td>GOLD group B: initial treatment</td>
<td>LABA or LAMA</td>
<td>plus</td>
<td>short-acting bronchodilator</td>
</tr>
<tr>
<td></td>
<td>plus</td>
<td>supportive care and advice</td>
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<tr>
<td></td>
<td>plus</td>
<td>pulmonary rehabilitation</td>
<td></td>
</tr>
<tr>
<td>GOLD group C: initial treatment</td>
<td>LAMA</td>
<td>plus</td>
<td>short-acting bronchodilator</td>
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<td>plus</td>
<td>supportive care and advice</td>
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<td></td>
<td>plus</td>
<td>pulmonary rehabilitation</td>
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</tr>
<tr>
<td>GOLD group D: initial treatment</td>
<td>LAMA or LABA/LAMA or LABA/ICS</td>
<td>plus</td>
<td>short-acting bronchodilator</td>
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<td></td>
<td>plus</td>
<td>supportive care and advice</td>
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<td></td>
<td>plus</td>
<td>pulmonary rehabilitation</td>
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## Ongoing Management

### (summary)

**GOLD group A, B, C, or D: persistent dyspnoea/exercise limitation after initial therapy**

<table>
<thead>
<tr>
<th>1st</th>
<th>LABA/LAMA or LABA/LAMA/ICS</th>
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</thead>
<tbody>
<tr>
<td>plus</td>
<td>short-acting bronchodilator</td>
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<tr>
<td>plus</td>
<td>supportive care and advice</td>
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<td>adjunct</td>
<td>pulmonary rehabilitation</td>
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<td>oxygen therapy and/or ventilatory support</td>
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<td>mucolytic</td>
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<td>adjunct</td>
<td>theophylline</td>
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<td>adjunct</td>
<td>bronchoscopic intervention or surgery</td>
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<td>adjunct</td>
<td>palliative care</td>
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</tbody>
</table>

**GOLD group A, B, C, or D: persistent exacerbations after initial therapy**

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<tr>
<th>1st</th>
<th>LABA/LAMA or LABA/ICS or LABA/LAMA/ICS</th>
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<tbody>
<tr>
<td>plus</td>
<td>short-acting bronchodilator</td>
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<tr>
<td>plus</td>
<td>supportive care and advice</td>
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<tr>
<td>adjunct</td>
<td>pulmonary rehabilitation</td>
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<tr>
<td>adjunct</td>
<td>oxygen therapy and/or ventilatory support</td>
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<td>adjunct</td>
<td>roflumilast</td>
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<td>adjunct</td>
<td>azithromycin</td>
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<td>adjunct</td>
<td>mucolytic</td>
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<td>adjunct</td>
<td>theophylline</td>
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<tr>
<td>adjunct</td>
<td>bronchoscopic intervention or surgery</td>
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<tr>
<td>adjunct</td>
<td>palliative care</td>
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</tbody>
</table>
Treatment algorithm

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

<table>
<thead>
<tr>
<th>GOLD group A: initial treatment</th>
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<tbody>
<tr>
<td><strong>1st short- or long-acting bronchodilator</strong></td>
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</tbody>
</table>

#### Primary options

**SABA**

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

**OR**

**SAMA**

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

**OR**

**LABA**

- **Salmeterol inhaled**: (50 micrograms/dose inhaler) 50 micrograms (1 puff) twice daily

**OR**

**LABA**

- **Indacaterol inhaled**: (75 microgram/capsule inhaler) 75 micrograms (1 capsule) once daily

**OR**

**LABA**

- **Arformoterol inhaled**: 15 micrograms nebulised twice daily

**OR**

**LABA**

- **Olodaterol inhaled**: (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily

**OR**

**LAMA**

- **Tiotropium inhaled**: (18 micrograms/capsule inhaler) 18 micrograms (1 capsule) once daily; (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily
Acute

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

OR

**LAMA**

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

OR

**LAMA**

» glycopyrronium inhaled: (55 micrograms/capsule inhaler) 55 micrograms (1 capsule) once daily
  Each capsule delivers 55 micrograms of glycopyrronium bromide (equivalent to 44 micrograms of glycopyrronium).

Global Initiative for Chronic Obstructive Lung Disease (GOLD) group A patients are characterised by few symptoms and low risk of exacerbations.

A short-acting bronchodilator or long-acting bronchodilator should be offered first line. Long-acting beta-2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are preferred over short-acting bronchodilators, except for patients with only occasional dyspnoea.[1] LABAs and LAMAs both significantly improve lung function, dyspnoea, and health status and reduce exacerbation rates. LAMAs have a greater effect on exacerbation reduction than LABAs.[1] [43] [44]

The effect of the bronchodilator should be evaluated. It should be continued if effective, otherwise it should be stopped and another class of bronchodilator or another inhaler device should be tried.[1] If a long-acting bronchodilator is prescribed, a short-acting bronchodilator should also be prescribed for rescue therapy. Regular use of short-acting bronchodilators is not generally recommended.

Short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) improve lung function and breathlessness and quality of life. Ipratropium, a SAMA, may have a small benefit over SABAs in improving health-related quality of life.[59]

SAMAs should be discontinued if a LAMA is prescribed.
Chronic obstructive pulmonary disease (COPD) Management

Acute

» SABAs include salbutamol. Ipratropium is a SAMA. LABAs include salmeterol, indacaterol, arformoterol, and olodaterol. LAMAs include tiotropium, umeclidinium, aclidinium, and glycopyrronium.

plus supportive care and advice

Treatment recommended for ALL patients in selected patient group

» Smoking cessation should be encouraged in all patients, in addition to guidance on avoiding exposure to occupational or environmental tobacco smoke and other irritants.[1] [2] Smoking cessation significantly reduces the rate of progression of COPD and risk of malignancies.

» Patients should be vaccinated against influenza virus and *Streptococcus pneumoniae*. [1] [130] Vaccination against influenza is associated with fewer exacerbations of COPD.[130] [131] The US Centers for Disease Control and Prevention (CDC) also recommends the tetanus/diphtheria/pertussis vaccine in people with COPD who were not vaccinated in adolescence.[134]

» Patients who use inhaled therapies should receive training on inhaler device technique. The majority of patients make at least one error in using their inhaler and incorrect inhaler use is associated with worse disease control.[114] [115] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[117]

» 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. 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. Self-management education should include provision of a written action plan. Physical activity is recommended for all patients with COPD.[1]

GOLD group B: initial treatment

1st LABA or LAMA

Primary options

LABA

» salmeterol inhaled: (50 micrograms/dose inhaler) 50 micrograms (1 puff) twice daily
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<tr>
<th>Acute</th>
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<td>OR</td>
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<tr>
<td>LABA</td>
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<tr>
<td>» indacaterol inhaled: (75 microgram/capsule inhaler) 75 micrograms (1 capsule) once daily</td>
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<td>OR</td>
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<tr>
<td>LABA</td>
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<td>» arformoterol inhaled: 15 micrograms nebulised twice daily</td>
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<td>OR</td>
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<tr>
<td>LABA</td>
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<tr>
<td>» olodaterol inhaled: (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily</td>
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<td>OR</td>
<td></td>
</tr>
<tr>
<td>LAMA</td>
<td></td>
</tr>
<tr>
<td>» tiotropium inhaled: (18 micrograms/capsule inhaler) 18 micrograms (1 capsule) once daily; (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily</td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>LAMA</td>
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</tr>
<tr>
<td>» umeclidinium inhaled: (62.5 micrograms/dose inhaler) 62.5 micrograms (1 puff) once daily</td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>LAMA</td>
<td></td>
</tr>
<tr>
<td>» aclidinium bromide inhaled: (400 micrograms/dose inhaler) 400 micrograms (1 puff) twice daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>LAMA</td>
<td></td>
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</tbody>
</table>
| » glycopyrronium inhaled: (55 micrograms/capsule inhaler) 55 micrograms (1 capsule) once daily  
Each capsule delivers 55 micrograms of glycopyrronium bromide (equivalent to 44 micrograms of glycopyrronium). |  |
| OR    |  |
| LAMA  |  |
### Acute

- **revefenacin inhaled:** 175 micrograms nebulised once daily

- Global Initiative for Chronic Obstructive Lung Disease (GOLD) group B patients are characterised by more symptoms and low risk of exacerbations.

- Either a long-acting muscarinic antagonist (LAMA) or a long-acting beta-2 agonist (LABA) may be prescribed. There is no evidence to recommend one class of long-acting bronchodilator over another for initial treatment in this group of patients. The choice should depend on the patient’s perception of symptom relief.[1] LABAs and LAMAs both significantly improve lung function, dyspnoea, and health status and reduce exacerbation rates. For patients with severe breathlessness, initial treatment with two bronchodilators of different classes may be warranted.[1]

- LABAs include salmeterol, indacaterol, arformoterol, and olodaterol. LAMAs include tiotropium, umeclidinium, aclidinium, and glycopyrronium. Revefenacin is a nebulised LAMA approved for the maintenance treatment of moderate to severe COPD.

  plus **short-acting bronchodilator**

  Treatment recommended for ALL patients in selected patient group

**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

- All patients diagnosed with COPD should be prescribed a short-acting bronchodilator for immediate symptom relief.[1] Short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) improve lung function and breathlessness and quality of life.

- Ipratropium, a SAMA, may have a small benefit over SABAs in improving health-related quality of life.[59] SAMAs should be discontinued if a LAMA is prescribed. SABAs include salbutamol.
### Acute

» Regular use of short-acting bronchodilators is not generally recommended. Failure to respond to short-acting bronchodilator may signify an acute exacerbation.

**plus** **supportive care and advice**

Treatment recommended for ALL patients in selected patient group

» Smoking cessation should be encouraged in all patients, in addition to guidance on avoiding exposure to occupational or environmental tobacco smoke or other irritants.[1] [2] Smoking cessation significantly reduces the rate of progression of COPD and risk of malignancies.

» Patients should be vaccinated against influenza virus and *Streptococcus pneumoniae*. [1] [130] Vaccination against influenza is associated with fewer exacerbations of COPD.[130] [131] The US Centers for Disease Control and Prevention (CDC) also recommends the tetanus/diphtheria/pertussis vaccine in people with COPD who were not vaccinated in adolescence.[134]

» Patients who use inhaled therapies should receive training on inhaler device technique. The majority of patients make at least one error in using their inhaler and incorrect inhaler use is associated with worse disease control.[114] [115] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[117]

» 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. 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. Self-management education should include provision of a written action plan. Physical activity is recommended for all patients with COPD.[1]

**plus** **pulmonary rehabilitation**

Treatment recommended for ALL patients in selected patient group

» Pulmonary rehabilitation compromises aerobic exercise, strength training, and education, and should be started early in the disease course. GOLD guidelines recommend pulmonary rehabilitation for patient groups B to D.[1]
### GOLD group C: Initial treatment

<table>
<thead>
<tr>
<th>1st</th>
<th>LAMA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» tiotropium inhaled: (18 micrograms/capsule inhaler) 18 micrograms (1 capsule) once daily; (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>» umeclidinium inhaled: (62.5 micrograms/dose inhaler) 62.5 micrograms (1 puff) once daily</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>» aclidinium bromide inhaled: (400 micrograms/dose inhaler) 400 micrograms (1 puff) twice daily</td>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>» glycopyrronium inhaled: (55 micrograms/capsule inhaler) 55 micrograms (1 capsule) once daily Each capsule delivers 55 micrograms of glycopyrronium bromide (equivalent to 44 micrograms of glycopyrronium).</td>
<td><strong>OR</strong></td>
</tr>
</tbody>
</table>
| » revfenacin inhaled: 175 micrograms nebulised once daily | **Global Initiative for Chronic Obstructive Lung Disease (GOLD) Group C patients have few symptoms and a higher risk of exacerbations.**

GOLD recommends starting a long-acting muscarinic antagonist (LAMA) in this group. LAMAs have a greater effect on exacerbation reduction than long-acting beta-2 agonists (LABAs) in patients with moderate to very severe COPD.**

**plus short-acting bronchodilator**

Treatment recommended for ALL patients in selected patient group
Management

Acute

Primary options

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

- All patients diagnosed with COPD should be prescribed a short-acting bronchodilator for immediate symptom relief.[1] Short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) improve lung function and breathlessness and quality of life.[59]

- Ipratropium, a SAMA, may have a small benefit over SABAs in improving health-related quality of life.[59] SAMAs should not be prescribed with a LAMA. SABAs include salbutamol.

- Regular use of short-acting bronchodilators is not generally recommended. Failure to respond to short-acting bronchodilator may signify an acute exacerbation.

**plus** supportive care and advice

Treatment recommended for ALL patients in selected patient group

- Smoking cessation should be encouraged in all patients, in addition to guidance on avoiding exposure to occupational or environmental tobacco smoke or other irritants.[1] [2] Smoking cessation significantly reduces the rate of progression of COPD and risk of malignancies.

- Patients should be vaccinated against influenza virus and *Streptococcus pneumoniae*. [1] [130] Vaccination against influenza is associated with fewer exacerbations of COPD.[130] [131] The US Centers for Disease Control and Prevention (CDC) also recommends the tetanus/diphtheria/pertussis vaccine in people with COPD who were not vaccinated in adolescence.[134]

- Patients who use inhaled therapies should receive training on inhaler device technique. The majority of patients make at least one error in using their inhaler and incorrect inhaler use is associated with worse disease control.[114] [115] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[117]

- 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
Chronic obstructive pulmonary disease (COPD) Management

Acute realistic. 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. Self-management education should include provision of a written action plan. Physical activity is recommended for all patients with COPD.\[1\]

plus pulmonary rehabilitation

Treatment recommended for ALL patients in selected patient group

» Pulmonary rehabilitation compromises aerobic exercise, strength training, and education, and should be started early in the disease course. GOLD guidelines recommend pulmonary rehabilitation for patient groups B to D.\[1\]

» Pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.\[137\]

GOLD group D: initial treatment

1st LAMA or LABA/LAMA or LABA/ICS

Primary options

LAMA

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

OR

LAMA

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

OR

LAMA

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

OR

LAMA

» glycopyrronium inhaled: (55 micrograms/capsule inhaler) 55 micrograms (1 capsule) once daily

Each capsule delivers 55 micrograms of glycopyrronium bromide (equivalent to 44 micrograms of glycopyrronium).
## Acute

<table>
<thead>
<tr>
<th>OR</th>
<th>LAMA</th>
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<tbody>
<tr>
<td></td>
<td>revefenacin inhaled: 175 micrograms nebulised once daily</td>
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<tr>
<th>OR</th>
<th>LABA/LAMA</th>
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<tbody>
<tr>
<td></td>
<td>umeclidinium/vilanterol inhaled: (62.5/25 micrograms/dose inhaler) 1 puff once daily</td>
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<tr>
<th>OR</th>
<th>LABA/LAMA</th>
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<tbody>
<tr>
<td></td>
<td>glycopyrronium/formoterol fumarate inhaled: (14.4/9.6 micrograms/dose inhaler) 1 puff twice daily</td>
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<tr>
<th>OR</th>
<th>LABA/LAMA</th>
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<tbody>
<tr>
<td></td>
<td>indacaterol/glycopyrronium inhaled: (110/50 micrograms/capsule inhaler) 1 capsule once daily</td>
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<th>OR</th>
<th>LABA/LAMA</th>
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<tr>
<td></td>
<td>tiotropium/olodaterol inhaled: (2.5/2.5 micrograms/dose inhaler) 2 puffs once daily</td>
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<tr>
<th>OR</th>
<th>LABA/LAMA</th>
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<tbody>
<tr>
<td></td>
<td>aclidinium bromide/formoterol fumarate inhaled: (400/12 micrograms/dose inhaler) 1 puff twice daily</td>
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<tr>
<th>OR</th>
<th>LABA/ICS</th>
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<tbody>
<tr>
<td></td>
<td>fluticasone furoate/vilanterol inhaled: (100/25 micrograms/dose inhaler) 1 puff once daily</td>
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<tr>
<th>OR</th>
<th>LABA/ICS</th>
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<tbody>
<tr>
<td></td>
<td>fluticasone propionate/salmeterol inhaled: (250/50 micrograms/dose inhaler) 1 puff twice daily</td>
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| OR |
Chronic obstructive pulmonary disease (COPD) Management

Acute

LABA/ICS

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

OR

LABA/ICS

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

- Global Initiative for Chronic Obstructive Lung Disease (GOLD) group D patients are characterised by more symptoms and high risk of exacerbations.

- GOLD recommends starting therapy with a long-acting muscarinic antagonist (LAMA), a long-acting beta-2 agonist (LABA)/LAMA combination, or an inhaled corticosteroid (ICS)/LABA combination.[1]

- LAMA is the first choice for most patients. A LABA/LAMA combination should be considered if the patient is highly symptomatic (COPD assessment test [CAT] score >20), especially if the patient has significant dyspnoea and/or exercise limitation.[1]

- An ICS/LABA combination should be considered if the patient’s blood eosinophil count is ≥300 cells/microlitre or the patient has a history of asthma.[1] The effect of treatment regimens containing ICS is higher in patients at higher risk of exacerbations (two or more exacerbations and/or one hospitalisation for an exacerbation in the previous year).[50] [52] [78] Blood eosinophil count may predict the effectiveness of adding inhaled corticosteroids to regular long-acting bronchodilator treatment to prevent exacerbations.[83] Little or no effect is seen at blood eosinophil counts of <100 cells/microlitre, while maximal effect is seen at blood eosinophil counts of >300 cells/microlitre.[46] [55] These thresholds indicate approximate cut-off values which may help clinicians predict the likelihood of a treatment benefit.[1] Use of ICS also slows the rate of decline in lung function following an exacerbation in patients with mild to moderate COPD and elevated blood eosinophils.[95] Former smokers are more corticosteroid-responsive than current smokers at any eosinophil count.[83] Both current and former smokers with COPD can benefit from ICS in terms of lung function and rates of exacerbations, although the effect is
Chronic obstructive pulmonary disease (COPD) Management

### Acute

smaller for heavy or current smokers compared with light or former smokers.[52] [84]

» Combination therapy with an inhaled corticosteroid and a LABA is superior to use of either agent alone.[93] [94] ICS increases the risk of developing pneumonia in some patients, so should only be used as initial therapy after the possible clinical risks and benefits have been evaluated.

» LAMAs include tiotropium, umeclidinium, aclidinium, and glycopyrronium. Umeclidinium/ vilanterol, glycopyrronium/formoterol, indacaterol/glycopyrronium, tiotropium/ olodaterol, and aclidinium/formoterol are LABA/LAMA combinations approved for use in COPD.[159] [78] Indacaterol/glycopyrronium showed superior efficacy compared with glycopyrronium or tiotropium in patients with moderate to severe COPD, and compared with salmeterol/fluticasone in preventing COPD exacerbation.[77] [78] Umeclidinium/vilanterol decreases the risk of exacerbations in patients with mild/moderate COPD.[74] LABA/ICS combinations include fluticasone furoate/ vilanterol, fluticasone propionate/salmeterol, budesonide/formoterol, and mometasone/ formoterol.

<table>
<thead>
<tr>
<th>plus short-acting bronchodilator</th>
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</thead>
<tbody>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
</tbody>
</table>

### Primary options

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

<table>
<thead>
<tr>
<th>OR</th>
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<tbody>
<tr>
<td>» ipratropium inhaled: (20 micrograms/dose inhaler) 40 micrograms (2 puffs) up to four times a day when required</td>
</tr>
</tbody>
</table>

» All patients diagnosed with COPD should be prescribed a short-acting bronchodilator for immediate symptom relief.[1] Short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) improve lung function and breathlessness and quality of life.[59]

» Ipratropium, a SAMA, may have a small benefit over SABAs in improving health-related quality of life.[59] SAMAs should be discontinued if a LAMA is prescribed. SABAs include salbutamol.
## Acute

» Regular use of short-acting bronchodilators is not generally recommended. Failure to respond to short-acting bronchodilator may signify an acute exacerbation.

**plus** supportive care and advice

Treatment recommended for ALL patients in selected patient group

» Smoking cessation should be encouraged in all patients, in addition to guidance on avoiding exposure to occupational or environmental tobacco smoke or other irritants. Smoking cessation significantly reduces the rate of progression of COPD and risk of malignancies.

» Patients should be vaccinated against influenza virus and *Streptococcus pneumoniae*. Vaccination against influenza is associated with fewer exacerbations of COPD. The US Centers for Disease Control and Prevention (CDC) also recommends the tetanus/diphtheria/pertussis vaccine in people with COPD who were not vaccinated in adolescence.

» Patients who use inhaled therapies should receive training on inhaler device technique. The majority of patients make at least one error in using their inhaler and incorrect inhaler use is associated with worse disease control. Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.

» 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. 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. Self-management education should include provision of a written action plan. Physical activity is recommended for all patients with COPD.

**plus** pulmonary rehabilitation

Treatment recommended for ALL patients in selected patient group

» Pulmonary rehabilitation compromises aerobic exercise, strength training, and education, and should be started early in the disease course. GOLD guidelines recommend pulmonary rehabilitation for patient groups B to D.
<table>
<thead>
<tr>
<th>Acute</th>
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<tbody>
<tr>
<td><strong>Pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.</strong> [137]</td>
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</tbody>
</table>
### Ongoing

**GOLD group A, B, C, or D: persistent dyspnoea/exercise limitation after initial therapy**

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<thead>
<tr>
<th>1st</th>
<th>LABA/LAMA or LABA/LAMA/ICS</th>
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<td><strong>Primary options</strong></td>
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<tr>
<td>LABA/LAMA</td>
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<tr>
<td>» <strong>umeclidinium/vilanterol inhaled:</strong> (62.5/25 micrograms/dose inhaler) 1 puff once daily</td>
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<td>OR</td>
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<tr>
<td>LABA/LAMA</td>
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<td>» <strong>glycopyrronium/formoterol fumarate inhaled:</strong> (14.4/9.6 micrograms/dose inhaler) 1 puff twice daily</td>
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<td>OR</td>
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<tr>
<td>LABA/LAMA</td>
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<tr>
<td>» <strong>tiotropium/olodaterol inhaled:</strong> (2.5/2.5 micrograms/dose inhaler) 2 puffs once daily</td>
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<td>OR</td>
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<tr>
<td>LABA/LAMA</td>
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<tr>
<td>» <strong>aclidinium bromide/formoterol fumarate inhaled:</strong> (400/12 micrograms/dose inhaler) 1 puff twice daily</td>
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<td>OR</td>
<td></td>
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<tr>
<td>LABA/LAMA/ICS</td>
<td></td>
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<tr>
<td>» <strong>fluticasone furoate/umeclidinium/vilanterol inhaled:</strong> (92/55/22 micrograms/dose inhaler) 1 puff once daily Each single inhalation provides a delivered dose of 92 micrograms of fluticasone furoate, 65 micrograms of umeclidinium bromide (equivalent to 55 micrograms of umeclidinium), and 22 micrograms of vilanterol (as trifenate).</td>
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<td>OR</td>
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</table>
Chronic obstructive pulmonary disease (COPD)

### Management

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</table>
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» 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: (55 micrograms/capsule inhaler) 55 micrograms (1 capsule) once daily  
Each capsule delivers 55 micrograms of glycopyrronium bromide (equivalent to 44 micrograms of glycopyrronium).  

» Global Initiative for Chronic Obstructive Lung Disease (GOLD) group A patients are characterised by few symptoms and low risk of exacerbations; group B by more symptoms and low risk of exacerbations; group C by few symptoms and a higher risk of exacerbations; and group D by more symptoms and high risk of exacerbations.[1]  

» GOLD advise that if a patient has both persistent symptoms and exacerbations after initial therapy, clinicians should follow the pathway for treating persistent exacerbations.[1]  

» Patients with persistent dyspnoea/exercise limitation while on a long-acting beta-2 agonist (LABA) or a long-acting muscarinic antagonist (LAMA) alone should switch to dual long-acting bronchodilator therapy with a LABA/LAMA combination. If symptoms do not improve, the second long-acting bronchodilator should be stopped. Changing inhaler device
Chronic obstructive pulmonary disease (COPD) Management

Ongoing

or molecules may be considered.[1] A LABA/LAMA combination may provide a better therapeutic effect without increasing the adverse effects of each class.[69] [70] [71] [72] Combination therapy with a LABA/LAMA reduces exacerbation rate compared with monotherapy. Once-daily LABA/LAMA delivered via a combination inhaler is more associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild/moderate COPD, compared with placebo.[74]

» Patients with persistent dyspnoea/exercise limitation while on combined LABA and inhaled corticosteroid (ICS) therapy may switch to LABA/LAMA/ICS. The indication for ICS should be reviewed. If the original indication was not appropriate, or if the patient has not responded to ICS treatment or experienced significant adverse effects, ICS should be withdrawn and the patient switched to a LABA/LAMA.[1] The combination may be provided in separate inhalers or a combination inhaler.

» Dyspnoea due to other causes should be considered, investigated, and treated. Inhaler technique and adherence should also be re-assessed, as these may have led to an inadequate response to treatment.

plus short-acting bronchodilator

Treatment recommended for ALL patients in selected patient group

Primary options

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

» All patients diagnosed with COPD should be prescribed a short-acting bronchodilator for immediate symptom relief.[1]

» Short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) improve lung function and breathlessness and quality of life.[59]

» Regular use of short-acting bronchodilators is not generally recommended. Failure to respond to short-acting bronchodilator may signify an acute exacerbation.

» SAMAs should not be prescribed with a LAMA. SABAs include salbutamol.

plus supportive care and advice

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## Ongoing

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</table>

| adjunct oxygen therapy and/or ventilatory support |
Chronic obstructive pulmonary disease (COPD) Management

Ongoing Treatment recommended for SOME patients in selected patient group

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

» Guidelines from the American Thoracic Society (ATS) recommend prescribing long-term oxygen therapy for at least 15 hours per day in adults with COPD who have severe chronic resting room air hypoxaemia. The ATS defines severe hypoxaemia as either: PaO₂ ≤7.3 kPa (55 mmHg) or oxygen saturation as measured by pulse oximetry (SpO₂) ≤88%; or PaO₂ 7.5-7.9 kPa (56-59 mmHg) or SpO₂ of 89% plus one of the following: oedema, haematocrit ≥55%, or P pulmonale on an ECG.[145]

» For patients prescribed home oxygen therapy, the ATS recommends that the patient and their caregivers should receive instruction and training on the use and maintenance of all oxygen equipment and education on oxygen safety, including smoking cessation, fire prevention, and tripping hazards.[145]

» Supplemental oxygen should be titrated to achieve SaO₂ ≥90%. [1] The patient should be reassessed after 60 to 90 days to determine whether oxygen is still indicated and is therapeutic.[1] Among different therapeutic modalities in COPD, the only two factors that improve survival are smoking cessation and oxygen supplementation.

» 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] [31]

» The ATS suggests prescribing ambulatory oxygen (oxygen delivered during exercise or activities of daily living) in adults with COPD who have severe exertional room air hypoxaemia.[145] However, the ATS suggests not prescribing long-term oxygen therapy in adults with COPD who have moderate chronic resting room air hypoxaemia (SpO₂ of 89%-93%).[145]
### Chronic obstructive pulmonary disease (COPD) Management

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>Adjunct</th>
<th>Primary options</th>
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</thead>
<tbody>
<tr>
<td>» For patients who have COPD and obstructive sleep apnoea, ventilatory support with continuous positive airway pressure (CPAP) can improve survival and reduce hospital admissions.[1][148] Non-invasive ventilation is occasionally used in patients with very severe but stable COPD, although the best selection criteria for candidates is unclear.[1][149]</td>
<td>mucolytic</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
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<td><strong>Primary options</strong></td>
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<td>» erdosteine: consult specialist for guidance on dose</td>
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<td>» acetylcysteine: consult specialist for guidance on dose</td>
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<td>» carbocisteine: consult specialist for guidance on dose</td>
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<td>Additional options</td>
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<td></td>
<td>theophylline</td>
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<td></td>
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</table>

For patients with the chronic bronchitis phenotype of COPD often produce thick sputum on a frequent basis. Mucolytic agents result in a small reduction in the frequency of acute exacerbations and in days of disability per month, but do not improve lung function or quality of life.[135] One meta-analysis comparing erdosteine, carbocisteine, and acetylcysteine concluded that erdosteine had the most favourable safety and efficacy profile. Erdosteine reduced the risk of hospitalisation due to an acute exacerbation, and erdosteine and acetylcysteine reduced the duration of an acute exacerbation.[136] Erdosteine is therefore the preferred option in countries where it is available. Treatment with mucolytic agents such as carbocisteine and acetylcysteine may be most beneficial for patients not on inhaled corticosteroids.[1] However, erdosteine may have a significant effect on mild exacerbations whether or not the patient is taking inhaled corticosteroids.[1]
Chronic obstructive pulmonary disease (COPD)

Management

Ongoing

» theophylline: consult specialist for guidance on dose

» Theophylline (a methylxanthine agent) is not commonly used because of limited potency, narrow therapeutic window, high risk profile, and frequent drug-drug interactions. Theophylline is indicated for persistent symptoms if inhaled therapy is insufficient to relieve airflow obstruction. Theophylline has modest effects on lung function in moderate to severe COPD.[107] GOLD advise that theophylline should only be used if other long-term bronchodilator treatments are unavailable or unaffordable.[1] Experts may prescribe theophylline after a patient has exhausted all options for inhaled therapies. Toxicity is dose-related.

adjunct bronchoscopic intervention or surgery

Treatment recommended for SOME patients in selected patient group

» Surgical interventions (bullectomy, lung volume reduction surgery,[150] [151] 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.[151] Lung volume reduction surgery is indicated in patients with very severe airflow limitation, and especially in patients with localised upper lobe disease and lower than normal exercise capacity.[150] 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. Endobronchial valve insertion can produce clinically meaningful improvements in appropriately selected patients with COPD.[152]

» Criteria for referral for lung transplantation include:[153]

» Progressive disease, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy.

» Patient is not a candidate for endoscopic or surgical lung volume reduction surgery (LVRS). Simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate.

» Body mass index, airflow Obstruction, Dyspnoea, and Exercise (BODE) index of 5 to 6.
**Ongoing**

- \( \text{PaCO}_2 > 50 \text{ mmHg or } 6.6 \text{ kPa and/or } \text{PaO}_2 < 60 \text{ mmHg or } 8 \text{ kPa.} \)
- FEV1 < 25% predicted.

**adjunct palliative care**

Treatment recommended for SOME patients in selected patient group

- Palliative therapies to improve symptoms of dyspnoea, offer nutritional support, address anxiety and depression, and reduce fatigue may benefit patients with COPD who experience these despite optimal medical therapy.[1] End-of-life care and hospice admission should be considered for patients with very advanced disease. 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.[152] Opioid analgesics, fans, neuromuscular electrical stimulation, and chest wall vibration can relieve dyspnoea.[1] Long-acting oral and parenteral opioids may be considered for treating dyspnoea in patients with severe COPD.[1] 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.[156]

- One Cochrane review concluded that there is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD.[157]

- Acupuncture and acupressure may also improve breathlessness and quality of life in patients with advanced COPD.[158]

**GOLD group A, B, C, or D: persistent exacerbations after initial therapy**

<table>
<thead>
<tr>
<th>1st</th>
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<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td>LABA/LAMA</td>
</tr>
<tr>
<td>- umeclidinium/vilanterol inhaled: (62.5/25 micrograms/dose inhaler) 1 puff once daily</td>
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<tr>
<td>Management</td>
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<td><strong>LABA/ICS</strong></td>
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<td><strong>LABA/ICS</strong></td>
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Chronic obstructive pulmonary disease (COPD)

Management

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Chronic obstructive pulmonary disease (COPD) Management

### Ongoing

- Symptoms and a higher risk of exacerbations; and group D by more symptoms and high risk of exacerbations.[1]

- Patients taking a long-acting beta-2 agonist (LABA) or long-acting muscarinic antagonist (LAMA) alone and who experience persistent exacerbations should increase therapy to either LABA/LAMA or LABA/inhaled corticosteroid (ICS).

- Blood eosinophil counts can identify patients who are more likely to respond to ICS.[46] LABA/ICS may be considered in patients with two or more moderate exacerbations per year, or at least one severe exacerbation needing hospital admission in the previous year, and an eosinophil count $\geq 100$ cells/microlitre, or if the history/clinical findings are suggestive of asthma.[1] Patients who have one exacerbation per year are more likely to respond to LABA/ICS if their peripheral eosinophil count is $\geq 300$ cells/microlitre.[47] Use of ICS also slows the rate of decline in lung function following an exacerbation in patients with mild to moderate COPD and elevated blood eosinophils.[95] Former smokers are more corticosteroid-responsive than current smokers at any eosinophil count.[83]

- Patients on LABA or LAMA who experience persistent exacerbations and who have blood eosinophils $<100$ cells/microliter or who have contraindications to ICS should commence a LABA/LAMA.[1]

- Patients who take LABA/LAMA who experience persistent exacerbations and whose blood eosinophils are $\geq 100$ cells/microlitre should escalate to LABA/LAMA/ICS.[1] Multiple studies support triple therapy with LABA/LAMA/ICS as being superior to single- or double-agent therapy with LABA/LAMA or LABA/ICS regarding rate of moderate to severe COPD exacerbations and rate of hospitalisation.[48] [49] [50] [51] [52] [53] [54] [55] [56] One randomised controlled trial has reported a reduction in all-cause mortality in patients at risk of exacerbations who take fluticasone furoate/umeclidinium/vilanterol, compared with umeclidinium/vilanterol.[96] Another randomised controlled trial had similar findings in terms of mortality in the triple therapy arm (budesonide/glycopyrronium/formoterol), but only at the higher dose of ICS.[56] For both studies, there were no differences in mortality compared with LABA/ICS.[56] [96] A post hoc pooled analysis of three trials of triple therapy in patients with COPD and severe airflow limitation and a history of exacerbations showed a non-
Chronic obstructive pulmonary disease (COPD)

Management

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>significant trend for lower mortality with triple therapy compared with non-ICS treatments.[97]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» American Thoracic Society guidelines recommend the use of LABA/LAMA/ICS in patients who have had one or more exacerbations requiring oral corticosteroids, antibiotics, or hospitalisation in the past year and who have symptoms of dyspnoea or reduced exercise tolerance despite LABA/LAMA dual therapy.[57] UK guidelines recommend the use of LABA/LAMA/ICS in patients who have an exacerbation requiring hospitalisation, or two moderate exacerbations within a year, despite dual therapy with LABA/LAMA.[2]</td>
</tr>
<tr>
<td></td>
<td>» Patients who take LABA/ICS and who experience persistent exacerbations should switch to LABA/LAMA/ICS.[1] If ICS is ineffective or causing significant adverse effects, patients may switch to LABA/LAMA. Patients with blood eosinophils ≥300 cells/microlitre are at greatest risk of exacerbations after withdrawing ICS.[58]</td>
</tr>
</tbody>
</table>

**plus**  
short-acting bronchodilator

Treatment recommended for ALL patients in selected patient group

**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 |

| » All patients diagnosed with COPD should be prescribed a short-acting bronchodilator for immediate symptom relief.[1] |
| » Short-acting beta-2 agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) improve lung function and breathlessness and quality of life.[59] Ipratropium, a SAMA, may have a small benefit over SABAs in improving health-related quality of life.[59] SAMAs should be discontinued if a LAMA is prescribed. SABAs include salbutamol. |

| » Regular use of short-acting bronchodilators is not generally recommended. Failure to respond to short-acting bronchodilator may signify an acute exacerbation. |
Ongoing

plus supportive care and advice

Treatment recommended for ALL patients in selected patient group

» Smoking cessation should be encouraged in all patients, in addition to guidance on avoiding exposure to occupational or environmental tobacco smoke or other irritants.[1] [2] Smoking cessation significantly reduces the rate of progression of COPD and risk of malignancies.

» Patients should be vaccinated against influenza virus and *Streptococcus pneumoniae*. [1] [130] Vaccination against influenza is associated with fewer exacerbations of COPD.[130] [131] The US Centers for Disease Control and Prevention (CDC) also recommends the tetanus/diphtheria/pertussis vaccine in people with COPD who were not vaccinated in adolescence.[134]

» Patients who use inhaled therapies should receive training on inhaler device technique. The majority of patients make at least one error in using their inhaler and incorrect inhaler use is associated with worse disease control.[114] [115] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[117]

» 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. 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. Self-management education should include provision of a written action plan. Physical activity is recommended for all patients with COPD.[1]

adjunct pulmonary rehabilitation

Treatment recommended for SOME patients in selected patient group

» Pulmonary rehabilitation compromises aerobic exercise, strength training, and education, and should be started early in the disease course. GOLD guidelines recommend pulmonary rehabilitation for patient groups B to D.[1]

» Pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.[137]
<table>
<thead>
<tr>
<th>Ongoing</th>
<th></th>
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<tbody>
<tr>
<td><strong>adjunct oxygen therapy and/or ventilatory support</strong></td>
<td></td>
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</table>

Treatment recommended for SOME patients in selected patient group

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

» Guidelines from the American Thoracic Society (ATS) recommend prescribing long-term oxygen therapy for at least 15 hours per day in adults with COPD who have severe chronic resting room air hypoxaemia. The ATS defines severe hypoxaemia as either: PaO₂ ≤7.3 kPa (55 mmHg) or oxygen saturation as measured by pulse oximetry (SpO₂) ≤88%; or PaO₂ 7.5-7.9 kPa (56-59 mmHg) or SpO₂ of 89% plus one of the following: oedema, haematocrit ≥55%, or P pulmonale on an ECG.[145]

» For patients prescribed home oxygen therapy, the ATS recommends that the patient and their caregivers should receive instruction and training on the use and maintenance of all oxygen equipment and education on oxygen safety, including smoking cessation, fire prevention, and tripping hazards.[145]

» Supplemental oxygen should be titrated to achieve SaO₂ ≥90%. The patient should be reassessed after 60-90 days to determine whether oxygen is still indicated and is therapeutic.[1] Among different therapeutic modalities in COPD, the only two factors that improve survival are smoking cessation and oxygen supplementation.

» 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] [31]

» The ATS suggests prescribing ambulatory oxygen (oxygen delivered during exercise or activities of daily living) in adults with COPD who have severe exertional room air hypoxaemia.[145] However, the ATS suggests not prescribing long-term oxygen therapy in adults with COPD who have moderate
Chronic obstructive pulmonary disease (COPD)

Management

Ongoing

- chronic resting room air hypoxaemia (SpO₂ of 89%-93%).[145]

  » For patients who have COPD and obstructive sleep apnoea, ventilatory support with continuous positive airway pressure (CPAP) can improve survival and reduce hospital admissions.[1] [148] Non-invasive ventilation is occasionally used in patients with very severe but stable COPD, although the best selection criteria for candidates is unclear.[1] [149]

  adjunct roflumilast

  Treatment recommended for SOME patients in selected patient group

  Primary options

  » roflumilast: 500 micrograms orally once daily

  » Roflumilast, an oral phosphodiesterase-4 inhibitor, may be prescribed for patients taking LABA/LAMA who have persistent exacerbations and whose blood eosinophils are <100 cells/microlitre, and for patients taking LABA/LAMA/ICS who have persistent exacerbations.[1]

  » Roflumilast should be considered in patients with FEV₁ <50% predicted and chronic bronchitis, particularly if they have had at least one hospitalisation for an exacerbation in the last year.[1]

  adjunct azithromycin

  Treatment recommended for SOME patients in selected patient group

  Primary options

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

  » Azithromycin may be prescribed for patients taking LABA/LAMA who have persistent exacerbations and whose blood eosinophils are <100 cells/microlitre, and for patients taking LABA/LAMA/ICS who have persistent exacerbations.[1]

  » Azithromycin increases the risk of colonisation with macrolide-resistant organisms and should not be prescribed for patients with hearing impairment, resting tachycardia, or apparent risk of QTc prolongation.[104] Azithromycin should be considered preferentially, but not only, in former smokers with persistent exacerbations despite appropriate therapy.[1]
Management

Ongoing

Before starting prophylactic antibiotics, baseline ECG and liver function tests should be performed, a sputum sample obtained for culture and sensitivity (including tuberculosis testing), the patient’s sputum clearance technique should be optimised, and bronchiectasis should be excluding with a CT scan.[2] [105] ECG and liver tests should be repeated after 1 month of treatment. Prophylactic antibiotic therapy should be reviewed at 6 and 12 months to determine whether there is a benefit in terms of exacerbation rates.[105] If antibiotic therapy is not effective it should be stopped.

adjunct mucolytic

Treatment recommended for SOME patients in selected patient group

Primary options

» erdosteine: consult specialist for guidance on dose

OR

» acetylcysteine: consult specialist for guidance on dose

OR

» carbocisteine: consult specialist for guidance on dose

Patients with the chronic bronchitis phenotype of COPD often produce thick sputum on a frequent basis. Mucolytic agents result in a small reduction in the frequency of acute exacerbations and in days of disability per month, but do not improve lung function or quality of life.[135] One meta-analysis comparing erdosteine, carbocisteine, and acetylcysteine concluded that erdosteine had the most favourable safety and efficacy profile. Erdosteine reduced the risk of hospitalisation due to an acute exacerbation, and erdosteine and acetylcysteine reduced the duration of an acute exacerbation.[136] Erdosteine is therefore the preferred option in countries where it is available. Treatment with mucolytic agents such as carbocisteine and acetylcysteine may be most beneficial for patients not on inhaled corticosteroids.[1] However, erdosteine may have a significant effect on mild exacerbations whether or not the patient is taking inhaled corticosteroids.[1]

adjunct theophylline
Chronic obstructive pulmonary disease (COPD) Management

Ongoing

Treatment recommended for SOME patients in selected patient group

Primary options

» theophylline: consult specialist for guidance on dose

Theophylline (a methylxanthine agent) is not commonly used because of limited potency, narrow therapeutic window, high risk profile, and frequent drug-drug interactions. Theophylline is indicated for persistent symptoms if inhaled therapy is insufficient to relieve airflow obstruction. Theophylline has modest effects on lung function in moderate to severe COPD.[107] GOLD advise that theophylline should only be used if other long-term bronchodilator treatments are unavailable or unaffordable.[1] Experts may prescribe theophylline after a patient has exhausted all options for inhaled therapies. Toxicity is dose-related.

adjunct bronchoscopic intervention or surgery

Treatment recommended for SOME patients in selected patient group

» Surgical interventions (bullectomy, lung volume reduction surgery,[150] [151] 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.[151] Lung volume reduction surgery is indicated in patients with very severe airflow limitation, and especially in patients with localised upper lobe disease and lower than normal exercise capacity.[150] 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. Endobronchial valve insertion can produce clinically meaningful improvements in appropriately selected patients with COPD.[152]

» Criteria for referral for lung transplantation include:[153]

» Progressive disease, despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy.

» Patient is not a candidate for endoscopic or surgical lung volume reduction surgery (LVRS). Simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate.
### Ongoing

- Body mass index, airflow Obstruction, Dyspnoea, and Exercise (BODE) index of 5 to 6.
- \( \text{PaCO}_2 >50 \text{ mmHg or 6.6 kPa and/or PaO}_2 <60 \text{ mmHg or 8 kPa.} \)
- \( \text{FEV}_1 <25\% \text{ predicted.} \)

### Lung transplantation

- Lung transplantation has been shown to improve quality of life and functional capacity.\(^{[151]}\) However, lung transplantation does not appear to confer a survival benefit.\(^{[154]}\)

### Palliative care

- Treatment recommended for SOME patients in selected patient group

- Palliative therapies to improve symptoms of dyspnoea, offer nutritional support, address anxiety and depression, and reduce fatigue may benefit patients with COPD who experience these despite optimal medical therapy.\(^{[1]}\) End-of-life care and hospice admission should be considered for patients with very advanced disease. 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.\(^{[155]}\) Opioid analgesics, fans, neuromuscular electrical stimulation, and chest wall vibration can relieve dyspnoea.\(^{[1]}\) Long-acting oral and parenteral opioids may be considered for treating dyspnoea in patients with severe COPD.\(^{[1]}\) 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.\(^{[156]}\)

- One Cochrane review concluded that there is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD.\(^{[157]}\)

- Acupuncture and acupressure may also improve breathlessness and quality of life in patients with advanced COPD.\(^{[158]}\)
Emerging

HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors are emerging medications in COPD that have been shown to improve some outcomes, with some improvement in lung function of patients with moderate to severe COPD.[160] Although retrospective studies showed decreased rate and severity of exacerbations, hospitalisation, and mortality in patients using statin therapy, especially in patients with co-existing cardiovascular disease (CVD) or hyperlipidaemia, a prospective study failed to prove this benefit.[161] In a meta-analysis of randomised controlled trials of patients with COPD taking statins, clinical outcomes were better in patients with co-existing CVD, elevated baseline C-reactive protein (CRP), or a high cholesterol level.[162] Another meta-analysis compared patients with COPD taking high-intensity statins with patients with COPD taking placebo. Use of statins resulted in a reduction in CRP and interleukin-6, but did not lead to significant difference in exercise capacity or quality of life.[163]

Other 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.[164] Long-term (≥6 months) treatment with acetylcysteine may decrease exacerbation prevalence but does not appear to affect exacerbation rate, lung volumes, or FEV1.[165] Antiplatelet therapy is associated with decreased all-cause mortality in patients with COPD, independent of cardiovascular risk.[166] Epidermal growth factor receptor kinase has potential to combat mucus overproduction. Therapy to inhibit fibrosis is being developed. There is also a search for serine protease and matrix metalloprotease inhibitors to prevent lung destruction and the subsequent development of emphysema, as well as drugs such as retinoid that may even reverse this process.[167] 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.[168] 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.[169] Many combinations of inhaler therapies are being introduced for COPD treatment. Aclidinium/formoterol is a long-acting muscarinic antagonist and long-acting beta-2 agonist (LABA/LAMA) combination therapy that is available in some countries, but is awaiting approval by the Food and Drug Administration (FDA) in the US.

Interventional therapies

Target lobe volume reduction, a novel technique for selective bronchoscopic lung volume resection, has now become available. In this technique, a one-way valve is inserted into the hyperinflated and emphysematous segment, leading to the collapse of the 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 patients with COPD who are likely to require surgery.[170] [171]

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.[172] [173]

Club cell protein 16 augmentation

Club cell protein 16 (CC16) is mainly produced by the Club cells (formerly known as Clara cells) in the respiratory tract epithelium. CC16 has anti-inflammatory properties in smoke-exposed lungs, and COPD is associated with CC16 deficiency. Experimental augmentation of CC16 levels reduces inflammation and cellular injury, and so CC16 augmentation may be a new disease-modifying treatment for COPD.[174]
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.[29] For disease due to occupational exposures, primary prevention is achieved by elimination or reduction of exposures in the workplace. Public health measures such as congestion charging, high occupancy vehicle lanes, and promoting walking or cycling can be implemented to reduce harm from air pollution.[30]

Secondary prevention

Vaccination against viral influenza and *Streptococcus pneumoniae* is strongly recommended in all patients with cardiopulmonary diseases, including COPD.[1] [191] [132] Vitamin D reduces the rate of moderate/severe exacerbations in patients with levels <25 nmol/L.[192] Levels should be checked in patients who are hospitalised with an exacerbation of COPD and supplementation should be given if levels are <25 nmol/L.[1]

Use of calcium supplementation 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.

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

Patient discussions

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

One Cochrane review found that self-management interventions that include an action plan for acute exacerbations of COPD are associated with improvements in health-related quality of life and fewer admissions to hospital for respiratory problems. An exploratory analysis found a small, but significantly higher, respiratory-related mortality rate for self-management compared to usual care, although no excess risk of all-cause mortality was seen.[108] Self-management plans should include personalised advice on: breathlessness and stress management techniques, energy conservation, avoiding aggravating factors, how to monitor symptoms, how to manage worsening symptoms, and contact information to use in the event of an exacerbation.[1]

Helping patients to self-manage should ideally address psychosocial concerns and patients’ personal beliefs about COPD and its management. Many patients report losses and limitations on their lifestyle and social interaction after a diagnosis of COPD. Symptoms of anxiety, depression, and frustration are common.[110] A systematic review found a small beneficial effect of cognitive behavioural therapy-based psychological treatment and symptoms of depression, compared with education or no intervention, although the evidence was limited by heterogeneity between trials and inability to blind participants and researchers to the intervention.[111]

One randomised controlled trial found that a telephone health coaching intervention to promote behaviour change in patients with mild COPD in primary care led to improvements in self-management activities, but did not improve health-related quality of life.[112] A meta-analysis found that health coaching that included goal setting, motivational interviewing, and COPD-related health education significantly improved health-related quality of life and reduced hospital admissions for an exacerbation of COPD, but did not decrease all-cause hospital admissions.[113]
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.

Physical activity is recommended for all patients with COPD and they should be encouraged to maintain it.[1] One systematic review and meta-analysis of randomised controlled trials found that exercise training on its own can improve physical activity in COPD, and greater improvements can be made with the addition of physical activity counselling.[121] Another systematic review and meta-analysis found that a combination of aerobic exercise and strength training was more effective than aerobic exercise alone in increasing leg muscle strength, but there was no difference between the groups in health-related quality of life, walking distance, or exercise capacity.[190] A Cochrane review found limited evidence for improvement in physical activity with physical activity counselling, exercise training, and pharmacological management of COPD. The authors commented that assessment of quality had been limited by lack of methodological detail and the diverse range of interventions had primarily been assessed in single studies.[123] The optimal timing, components, duration, and models for improving physical activity remain unclear. Meta-analyses suggest that yoga and Qigong can improve exercise capacity and pulmonary function in patients with COPD.[124] [125]

Patients who use inhaled therapies should receive training on inhaler device technique. The majority of patients make at least one error in using their inhaler and incorrect inhaler use is associated with worse disease control.[114] [115] Poor technique is more likely when patients are using multiple devices or have never received inhaler technique training.[116] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[117] Demonstration using a placebo device may be most effective for teaching inhaler technique to adults aged ≥65 years.[118] Patients should be asked to bring their inhalers to clinic to facilitate a review of inhaler use.[1] Pharmacist-led interventions and lay health coaching can improve inhaler technique and adherence in patients with COPD.[119] [120]
Monitoring

Patients with COPD should be evaluated on a regular basis depending on the severity of disease. Mild stable COPD patients may be followed up at 6-month intervals, while patients with severe frequent exacerbations, and recently 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, inhaler technique, adverse effects of 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. These can be found in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[1]

Smoking status and smoke exposure should be determined at each appointment, followed by appropriate action.[1]

The GOLD guidelines recommend measuring FEV1 by spirometry at least once a year to identify patients who are declining quickly.[1] Functional capacity should be measured by a timed walking test. Oxygen saturation should be monitored and patients evaluated periodically for the need of supplemental oxygen. Imaging may be indicated if symptoms have worsened; patients with repeated exacerbation characterised by purulent sputum should be investigated for bronchiectasis.[1]

Patients need to be monitored for short-term and long-term complications of COPD and for comorbidities. Patient weight, nutrition status, and physical activity should also be monitored. Cachexia and reduced physical performance are indicators of a poor prognosis.
Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>cor pulmonale</td>
<td>long term</td>
<td>high</td>
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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. Therapy for COPD should be optimised. Judicious use of diuretics is warranted.[186]

| lung cancer            | long term | medium     |

COPD is a risk factor for lung cancer independently of tobacco exposure. A population-based cohort study found that compared with never smokers without COPD, the fully-adjusted hazard ratios for lung cancer in never smokers with COPD, ever smokers without COPD, and ever smokers with COPD were 2.67, 1.97, and 6.19, respectively.[189]

| recurrent pneumonia    | variable  | high       |

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.[183] [184]

Use of antibiotic therapy has shown some benefit.[185] 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 patients with COPD.

| depression             | variable  | high       |

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

| pneumothorax           | variable  | medium     |

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.
### Chronic obstructive pulmonary disease (COPD)

#### Follow up

<table>
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<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>Chest CT: severe COPD changes with right pneumothorax</td>
<td>variable</td>
<td>medium</td>
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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 thoracoscopy pleurodesis or bullectomy, are warranted.

<table>
<thead>
<tr>
<th>respiratory failure</th>
<th>variable</th>
<th>medium</th>
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<tr>
<td>A study of a large number of patients with COPD and acute respiratory failure reported in-hospital mortality of 17% to 49%. [182] Therapy includes non-invasive positive pressure ventilation and/or mechanical ventilation.</td>
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<table>
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<tr>
<th>anaemia</th>
<th>variable</th>
<th>medium</th>
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<tr>
<td>Anaemia is more prevalent than previously thought, affecting almost 25% of patients with COPD. [187] A low haematocrit indicates a poor prognosis in patients receiving long-term oxygen treatment. [188]</td>
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### Prognosis

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

Although short-term survival for patients with COPD and respiratory failure depends on the overall severity of acute illness, long-term survival is primarily influenced by the severity of COPD and the presence of comorbid conditions. Traditionally, prognosis has been reported based on the FEV1, which is a part of pulmonary function testing. A meta-regression analysis showed a significant correlation between increased FEV1 and lower risk of COPD exacerbation.[175]

In addition to the FEV1, other factors that predict prognosis are weight (very low weight is a negative prognostic factor[176]), distance walked in 6 minutes, and degree of shortness of breath with activities. These factors, known as the Body mass index, airflow Obstruction, Dyspnoea, and Exercise (BODE) index, can be used to provide information on prognosis for 1-year, 2-year, and 4-year survival.[177] One study revealed that plasma pro-adrenomedullin concentration plus BODE index is a better prognostic tool than BODE index alone.[178] Elevation of adrenomedullin, arginine vasopressin, atrial natriuretic peptide, and C-reactive protein[179] is associated with increased risk of death in patients with stable COPD.[180] UK guidelines do not recommend using the BODE index to assess prognosis.[2]

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 patients with COPD.[181] Frequent COPD exacerbations and requirement for multiple intubation and invasive mechanical ventilation for acute respiratory failure in patients with COPD are markers of poor prognosis.[182]

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

#### Europe

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

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

#### International

**Global strategy for the diagnosis, management, and prevention of COPD** (https://goldcopd.org/2021-gold-reports/)

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

### Treatment guidelines

#### Europe


*Published by:* British Thoracic Society  
*Last published:* 2020

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

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


*Published by:* Swiss Respiratory Society; European Association for Bronchology and Interventional Pulmonology  
*Last published:* 2019

**BTS/ICS guidelines for the ventilatory management of acute hypercapnic respiratory failure in adults** (https://www.brit-thoracic.org.uk/quality-improvement/guidelines/niv/)

*Published by:* British Thoracic Society; Intensive Care Society  
*Last published:* 2017
<table>
<thead>
<tr>
<th>Region</th>
<th>Guidelines</th>
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<tbody>
<tr>
<td><strong>International</strong></td>
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<tr>
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<td><strong>Global strategy for the diagnosis, management, and prevention of COPD (<a href="https://goldcopd.org/2021-gold-reports/">https://goldcopd.org/2021-gold-reports/</a>)</strong></td>
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Online resources

Key articles


References


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Chronic obstructive pulmonary disease (COPD)


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Chronic obstructive pulmonary disease (COPD)


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Images

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

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Figure 2: COPD chest x-ray (lateral view): hyperinflated lung, flattened diaphragm, increased antero-posterior diameter (barrel chest) in lateral view

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Figure 3: COPD chest CT: hyperinflated lung, emphysematous changes, and increased antero-posterior diameter (barrel chest)

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Figure 4: Chest CT: severe COPD changes with right pneumothorax

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

Figure 1 – BMJ Best Practice Numeral Style
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