BMJ Best Practice

Chronic obstructive pulmonary disease (COPD)

Straight to the point of care

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Summary

Chronic obstructive pulmonary disease (COPD) is 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 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. Pulmonary rehabilitation improves exercise tolerance, dyspnea, and health-related quality of life, and reduces rehospitalizations and mortality.

Long-term oxygen therapy improves survival in severe COPD.

Definition

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease state characterized by chronic respiratory symptoms and airflow limitation that is not fully reversible. It encompasses emphysema, bronchiolitis, and chronic bronchitis. The airflow limitation is often 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 the third leading cause of death worldwide, causing 3.23 million deaths in 2019, with 90% of deaths in low- and middle-income countries.[1] [9] [10] [11] [12] Globally, deaths from COPD increased by 23% from 1990 to 2017 and COPD and related deaths are estimated to increase to 5.4 million by 2060.[1] [13] COPD is more common in older people, especially those ages 65 years and older.[14] The prevalence of COPD in the US was estimated at 14% postbronchodilator test results based on data from 2007 to 2010.[15] The death rate due to COPD in the US increased over 100% between 1969 and 2013.[16] A 2019 National Health Interview Survey revealed that the prevalence of COPD in US adults was greater in those living in non-metropolitan areas than in metropolitan areas, at 8.0% and 4.0%, respectively.[17] 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.[18]

Previously, most studies reported that the prevalence and mortality of COPD are greater in men than in women.[13] However, data from 2012 to 2013 from developed countries suggest that COPD prevalence is now almost equal in men and women, probably due to different patterns of cigarette smoking.[19] Some studies have also suggested that women may have a greater risk of airflow obstruction than men despite exposure to a similar dose of tobacco.[20]

An international study reported that the prevalence of COPD in never-smokers is 12.2%.[21] 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 such as in the mining industry and in food preparation and serving.[22] [23]

Etiology

Tobacco smoking is the main risk factor for COPD.[1] [13] Tobacco smoking causes over 70% of COPD cases in high-income countries and 30% to 40% of cases in low- and middle-income countries.[24] Smoking exerts its effect by causing an inflammatory response, cilia dysfunction, and oxidative injury.[25]

Air pollution, indoor burning of biomass fuels, and occupational exposure to dusts, chemical agents, and fumes are other etiologies.[26] [27] [28] Inhalation of high doses of pesticides is linked to increased incidence of COPD, as are high levels of particulate matter.[29] [30] [31] [32] 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.[33] The risk of developing COPD can be increased by processes that affect optimal lung growth and therefore lung function.[34] These processes may go back as far as gestation, birth, childhood, and adolescence. For example, there is a positive association between birthweight and FEV_1 in adulthood. Disadvantageous factors in childhood may be as important as heavy smoking in predicting lung function in adulthood.[35] [36]

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 physiologic changes. The inflammatory and structural changes in the lung increase with disease severity and persist after smoking cessation.[33]

The main components of these changes are narrowing and remodeling of airways, increased number of goblet cells, enlargement of mucus-secreting glands of the central airways, 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. Airway remodeling 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.[33] Growing evidence implicates eosinophils, a leukocyte usually involved in allergic disease, in the COPD inflammatory cascade.[37]

Elastin breakdown and subsequent loss of alveolar integrity causes emphysema.[38] [39] Ciliary dysfunction and increased goblet cell size and number lead to excessive mucus secretion.

Increased airway resistance is the physiologic definition of COPD. Decreased elastic recoil, fibrotic changes in lung parenchyma, and luminal obstruction of airways by secretions all contribute to increased airways resistance. Expiratory flow limitation promotes hyperinflation. Hyperinflation and destruction of lung 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.[1] [40] 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] [6]

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 edema.

Case history #2

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

Other presentations

Some patients report chest tightness, which often follows exertion and may arise from intercostal muscle contraction. Weight loss, muscle loss, and anorexia are common in patients with severe and very severe COPD.[1] Other presentations include fatigue, hemoptysis, cyanosis, and morning headaches secondary to hypercapnia. Chest pain and hemoptysis 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 edema and hepatomegaly secondary to cor pulmonale, and asterixis secondary to hypercapnia.

Patients may also present with signs and symptoms of COPD complications. These include severe shortness of breath, severely decreased air entry, and chest pain secondary to an acute COPD exacerbation or spontaneous pneumothorax.[3] [4] Patients with COPD often have other comorbidities, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome and diabetes, osteoporosis, depression, anxiety, lung cancer, gastroesophageal reflux disease, bronchiectasis, obstructive sleep apnea, and cognitive impairment.[1] [5] [6]

One UK study found that 14.5% of patients with COPD had a concomitant diagnosis of asthma, whereas a global meta-analysis estimated the pooled prevalence of asthma in patients with COPD to be 29.6% (range: 12.6% to 55.5%).[7] [8]

Approach

History

COPD has an insidious onset and usually presents in older people. A history of productive cough, wheezing, and shortness of breath, particularly with exercise, is typical. Other symptoms include frequent bronchitis, reduced exercise tolerance, waking at night with breathlessness, ankle swelling, and fatigue.[1] [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 hospitalizations should be sought.

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

Physical exam

A physical exam is not diagnostic of COPD but is an important part of patient care.[1] Examination may show tachypnea, respiratory distress, use of accessory muscles, and intercostal retraction. Barrel chest is a common observation. There may be hyperresonance on percussion, and distant breath sounds and poor air movement on auscultation. Wheezing, coarse crackles, clubbing, and cyanosis, as well as signs of right-side heart failure (distended neck veins, loud P2, hepatomegaly, hepatojugular reflux, and lower-extremity edema), may be present. Occasionally patients may exhibit asterixis - loss of postural control in the outstretched arms (commonly known as a flap) caused by hypercapnia. This is due to impaired gas exchange in lung parenchyma, worsens with exercise, and is suggestive of respiratory failure.

Initial tests

Spirometry is required to make the diagnosis of COPD and is also used for monitoring disease progress.[1] [2] [66] 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 minimize variability.[1] Patients with COPD have a distinctive pattern seen on spirometry, with a reduced FEV_1 and FEV_1/FVC ratio. The presence of airflow limitation is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria as a postbronchodilator FEV_1/FVC <0.7.[1] In cases where FVC may be hard to measure, FEV_6 (forced expiratory volume at 6 seconds) can be used.[67] Spirometry also indicates the severity of airflow obstruction. In patients with an FEV_1/FVC ratio <0.7:[1]

- FEV_1 ≥80% predicted indicates mild COPD (GOLD 1)
- FEV_1 <80% and ≥50% predicted indicates moderate COPD (GOLD 2)
- FEV_1 <50% and ≥30% predicted indicates severe COPD (GOLD 3)
- FEV_1 <30% predicted indicates very severe COPD (GOLD 4).

Chest x-ray is rarely diagnostic but should be performed to exclude other diagnoses and to assess for the presence of significant comorbidities.[1] [68]

Pulse oximetry screens for hypoxia and should be performed in all patients presenting with signs of respiratory failure or right heart failure. If peripheral arterial oxygen saturation is ≤92%, then arterial blood gases should be measured.[1]

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

The Modified British Medical Research Council (mMRC) questionnaire or the COPD Assessment Test (CAT) are recommended to assess symptoms. GOLD cautions against the use of the mMRC dyspnea scale alone for assessing patients, as symptoms of COPD go beyond dyspnea alone. For this reason, the CAT is preferred. However, GOLD acknowledges that the use of the mMRC scale is widespread, and so a threshold of an mMRC grade ≥2 is still included to define "more breathless" patients, as opposed to "less breathless" patients, in its assessment criteria.[1]

The best predictor of frequent exacerbations (two or more per year) is a history of previously treated exacerbations.[69]

The GOLD guidelines uses a combined "ABE" approach to assess patients according to their level of symptoms and previous history of exacerbations. Symptoms are assessed using the mMRC or CAT scale. Exacerbations are assessed independently of symptoms to highlight their clinical relevance.[1]

- Group A: low risk (0-1 exacerbations per year, not requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT <10)
- Group B: low risk (0-1 exacerbations per year, not requiring hospitalization) and more symptoms (mMRC ≥2 or CAT ≥10)
- Group E: high risk (≥2 exacerbations per year, or ≥1 requiring hospitalization) and any level of symptoms.

UK guidelines recommend a complete blood count (CBC) for all newly diagnosed patients to screen for anemia or polycythemia.[2]

Other tests

Detailed pulmonary function tests performed in specialist pulmonary function laboratories can measure flow volume loops and inspiratory capacity. They are not used routinely but can be helpful in resolving diagnostic uncertainties and for preoperative assessment. Diffusing capacity of the lung for carbon monoxide (DLCO) was previously only measured in specialist laboratories; however, portable systems are now available, allowing measurements to be taken in the field. International guidelines from GOLD recommend a DLCO measurement if a patient with COPD has dyspnea that is disproportionate to their degree of airflow obstruction. A low DLCO value (<60% predicted) in a patient with COPD is associated with decreased exercise capacity, worse health status, and increased risk of death.[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.[1] All patients with a diagnosis of COPD should be screened once, especially in areas with high prevalence of alpha-1 antitrypsin deficiency.[70] [71] This may aid in family screening and counseling.[1]

GOLD guidelines recommend consideration of computed tomography (CT) scan for patients with persistent exacerbations, those with symptoms that do not correspond with disease severity on lung

function testing, those with FEV_1 <45% of predicted with significant hyperinflation, and those meeting criteria for lung cancer screening.[1] Annual low-dose CT scan (LDCT) is recommended by the US Preventive Services Task Force (USPSTF) for lung cancer screening in patients with COPD that is due to smoking.[72]

Obstructive sleep apnea is associated with increased risk of death and hospitalization in patients with COPD, and a sleep study should be considered.[73]

Exercise testing can be useful in patients with a disproportional degree of dyspnea.[1] 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).[74] Exercise testing is also of use in selecting patients for rehabilitation. Respiratory muscle function may also be tested if dyspnea or hypercapnia are disproportionately increased with respect to FEV_1, as well as in patients with poor nutrition and those with corticosteroid myopathy.[75]

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

Risk factors for COPD are similar to those for ischemic heart disease, so comorbidity is common. ECG may detect right ventricular hypertrophy, arrhythmia, or ischemia. Echocardiogram evaluates suspected cardiac disease or pulmonary hypertension.[2]

The WHO has specified a minimum set of interventions for the diagnosis of 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)

Presence of high circulatory eosinophils predicts higher risk of exacerbations and predicts good response in preventive and therapeutic effects of corticosteroids. Blood eosinophil counts can identify patients who are more likely to respond to inhaled corticosteroids (ICS).[76] [77] [78] They may predict the effectiveness of adding ICS to regular long-acting bronchodilator treatment to prevent exacerbations.[77] [78] [79] Little or no effect is seen with ICS at blood eosinophil counts of <100 cells/microliter, while maximal effect is seen at blood eosinophil counts of ≥300 cells/microliter.[76] [80] These thresholds indicate approximate cut-off values that may help clinicians predict the likelihood of ICS treatment benefit.[1] Patients with blood eosinophils ≥300 cells/microliter are at greatest risk of exacerbations after withdrawing ICS.[81]

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.

hyperresonance on percussion (common)

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

distant breath sounds on auscultation (common)

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

poor air movement on auscultation (common)

- Secondary to loss of lung elasticity and lung tissue breakdown.

wheezing on auscultation (common)

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

coarse crackles (common)

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

tachypnea (uncommon)

- An increased respiratory rate occurs to compensate for hypoxia and hypoventilation.
- May involve use of accessory muscles.

asterixis (uncommon)

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

distended neck veins (uncommon)

- Occurs secondary to increased intrathoracic pressure and cor pulmonale.

lower-extremity swelling (uncommon)

- Suggests cor pulmonale and secondary pulmonary hypertension as a complication of advanced chronic lung disease.

fatigue (uncommon)

- Occurs because of disrupted sleep secondary to constant nocturnal cough and persistent hypoxia and hypercapnia.

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)

- 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.[1] [13] Tobacco smoking causes over 70% of COPD cases in high-income countries and 30% to 40% of cases in low- and middle-income countries.[24]

- Passive exposure to cigarette smoke increases risk of COPD.[41]
- There is some evidence that vaping leads to worse pulmonary-related health outcomes in people with or at risk of COPD.[42] [43] However, it remains unclear if e-cigarettes are an independent risk factor for COPD.[1] [44]

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 FEV_1.

genetic factors

- Airway responsiveness to inhaled insults depends on genetic factors.
- Alpha-1 antitrypsin deficiency, a genetic disorder encountered in people of northern European ancestry, causes panacinar emphysema in lower lobes at a young age. One European study estimated that approximately 1 in every 850 patients with COPD has an alpha-1 antitrypsin protease inhibitor ZZ genotype, which is associated with severe disease.[45]
- One systematic review and meta-analysis found that the prevalence of COPD in adult offspring of people with COPD is greater than population-based estimates.[46]

lung growth and development

- The risk of developing COPD can be increased by processes that affect optimal lung growth and therefore lung function.[34] These processes may go back as far as gestation, birth, childhood, and adolescence. For example, there is a positive association between birthweight and FEV_1 in adulthood. Disadvantageous factors in childhood may be as important as heavy smoking in predicting lung function in adulthood.[35] [36]
- Frequent childhood infection may cause scarring of lungs, decrease elasticity, and increase risk for COPD. History of tuberculosis is associated with increased risk of COPD.[47]

Weak

white ancestry

- COPD is more common in white people than in black and South Asian people, after adjusting for smoking, age, sex, and socioeconomic status.[48]

exposure to air pollution

- Chronic exposure to dust, traffic exhaust fumes, sulfur dioxide, nitrogen dioxide, and particulate matter increases risk of COPD.[13] [26] [27]

exposure to burning solid or biomass fuel

- Household exposure to burning coal or biomass fuel increases the risk of COPD.[49]

occupational exposure to dusts, chemicals, pesticides, vapors, fumes, or gases

- Approximately 14% of all cases of COPD are attributable to occupational exposure.[28] [50]

male sex

- COPD is more common in men, likely due to more smokers being male.[19] However, there is a suggestion that women may be more susceptible than men to the effects of tobacco smoke.[51] [52] [53]

low socioeconomic status

- The risk for developing COPD is increased in people with lower socioeconomic status.[11] [12] However, this may reflect exposure to cigarette smoke, pollutants, or other factors.

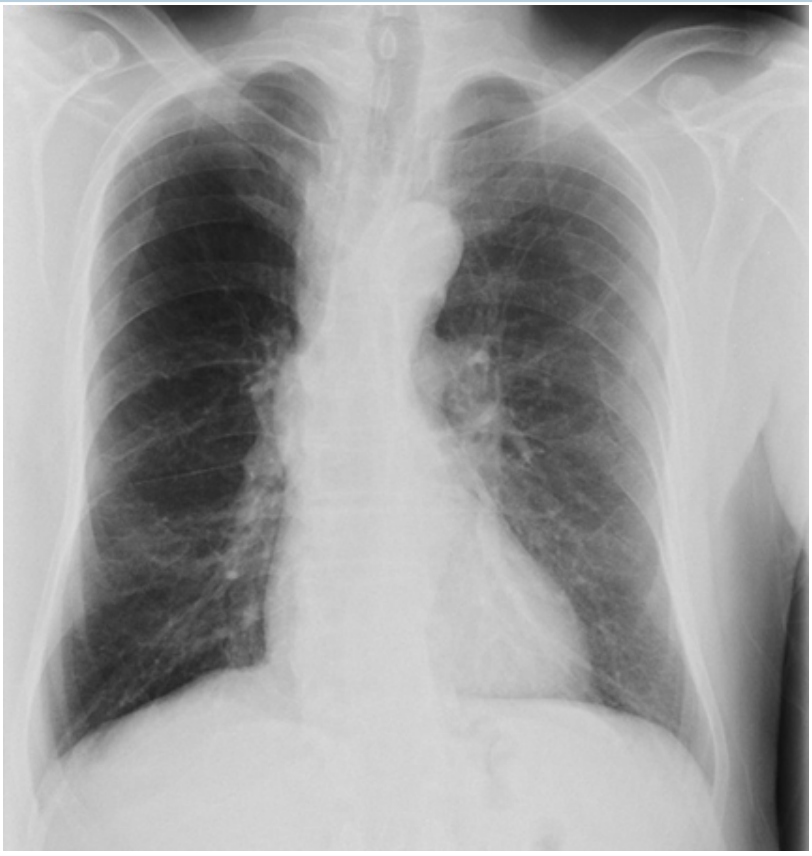
rheumatoid arthritis

- Epidemiologic studies indicate an association between risk of COPD and history of rheumatoid arthritis.[47] One 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.[54]

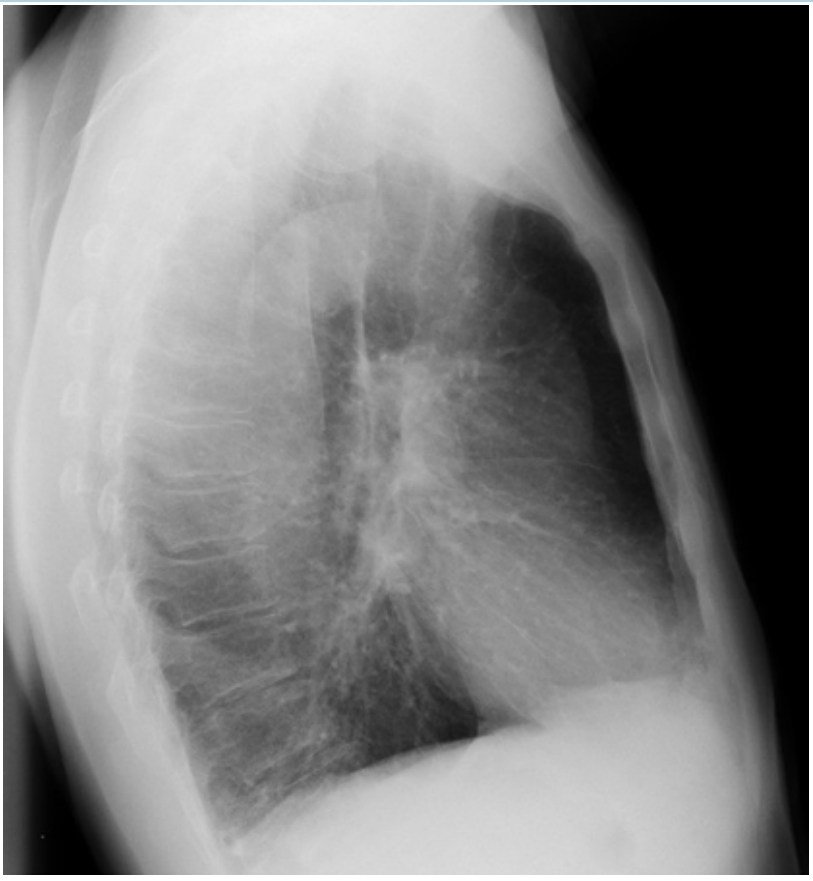
Tests

1st test to order

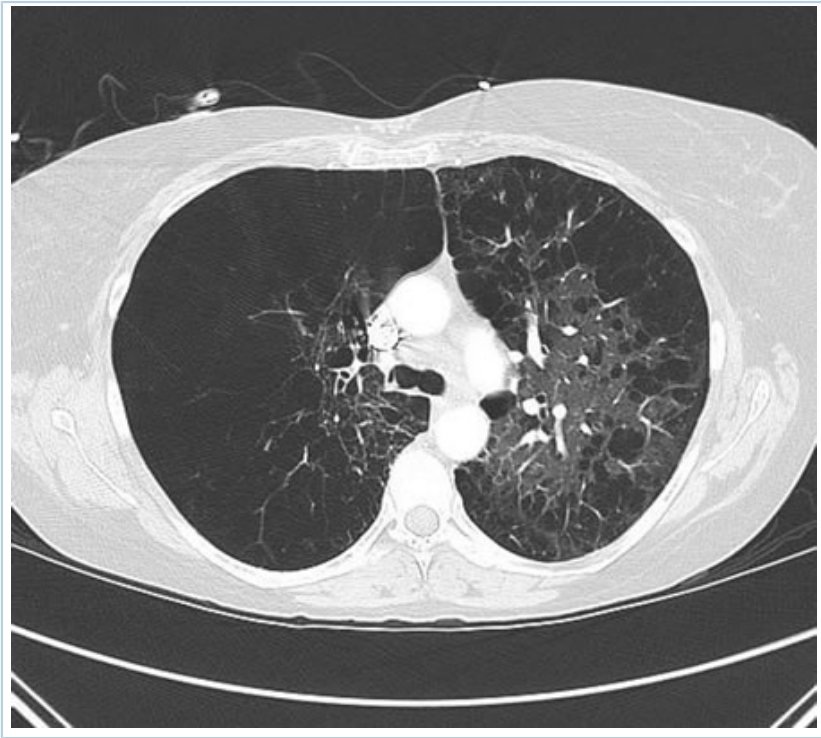
Test	Result
spirometry • Test establishes FEV_1 and FVC. The ratio of these two values indicates whether airflow obstruction is present. COPD severity is classified based on the patient's FEV_1 and its percentage of the predicted FEV_1. In cases where FVC may be hard to measure, FEV_6 (forced expiratory volume at 6 seconds) can be used.[67] • Spirometry should be performed after administering an adequate dose of at least one short-acting inhaled bronchodilator to minimize variability.[1] •	**FEV_1/FVC ratio <0.7; total absence of reversibility is neither required nor the most typical result**
standardized symptoms score • In addition to airflow limitation, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recognize the importance of exacerbations in affecting the natural course of COPD, and place emphasis on assessment of symptoms, risk factors for exacerbations, and comorbidities.[1] • The Modified British Medical Research Council (mMRC) questionnaire or the COPD Assessment Test (CAT) are recommended to assess symptoms. GOLD cautions against the use of the mMRC dyspnea scale alone for assessing patients, as symptoms of COPD go beyond dyspnea alone. For this reason, the CAT is preferred. However, GOLD acknowledges that the use of the mMRC scale is widespread, and so a threshold of an mMRC grade ≥2 is still included to define "more breathless" patients, as opposed to "less breathless" patients, in its assessment criteria.[1]	**mMRC score ranges from 0-4; CAT score ranges from 0-40: mMRC ≥2 or CAT score ≥10 indicates higher symptoms burden**
pulse oximetry • Checked as part of vital signs on acute presentation. A good pulse wave should be picked up by the device. In patients with chronic disease, an oxygen saturation of 88% to 90% may be acceptable. • If ≤92%, arterial blood gases (ABG) should be checked.[1]	**low oxygen saturation**
ABG • Checked in patients who are acutely sick, especially if they have an abnormal pulse oximetry reading. Should also be performed in stable patients with FEV_1 <35% predicted or with clinical signs suggestive of respiratory failure, or if peripheral arterial oxygen saturation is ≤92%. • Hypercapnia, hypoxia, and respiratory acidosis are signs of impending respiratory failure and possible need for intubation.	**$PaCO_2$ >50 mmHg and/or PaO_2 of <60 mmHg suggests respiratory insufficiency**
Chest x-ray • Seldom diagnostic, but useful in ruling out other pathologies and in assessing for the presence of significant comorbidities (e.g., pulmonary fibrosis, cardiomegaly).[1] • Increased anteroposterior ratio, flattened diaphragm, increased intercostal spaces, and hyperlucent lungs may be seen.	**hyperinflation**

Test	Result
	

COPD chest x-ray (AP view): hyperinflated lung, flattened diaphragm, increased intercostal spaces
From the collection of Manoochehr Abadian Sharifabad, MD

Test	Result
 *COPD chest x-ray (lateral view): hyperinflated lung, flattened diaphragm, increased antero-posterior diameter (barrel chest) in lateral view* *From the collection of Manoochehr Abadian Sharifabad, MD* • May also demonstrate complications of COPD, such as pneumonia and pneumothorax.	
CBC • This test may be considered to assess severity of an exacerbation and may show polycythemia (hematocrit >55%), anemia, and leukocytosis. UK guidelines advise CBC in all newly diagnosed patients.[2]	**elevated hematocrit, anemia, possible increased WBC count**

Other tests to consider

Test	Result
pulmonary function tests • Detailed pulmonary function tests performed in specialist pulmonary function laboratories can measure flow volume loops and inspiratory capacity. They are not used routinely but can be helpful in resolving diagnostic uncertainties and for preoperative assessment. • Diffusing capacity of the lung for carbon monoxide (DLCO) was previously only measured in specialist laboratories; however, portable systems are now available, allowing measurements to be taken in the field. International guidelines from GOLD recommend a DLCO measurement if a patient with COPD has dyspnea that is disproportionate to their degree of airflow obstruction. A low DLCO value (<60% predicted) in a patient with COPD is associated with decreased exercise capacity, worse health status, and increased risk of death.[1]	**obstructive pattern, decreased DLCO (<60% predicted)**
chest CT scan • Provides better visualization of type and distribution of lung tissue damage and bulla formation than chest x-ray.  *COPD chest CT: hyperinflated lung, emphysematous changes, and increased antero-posterior diameter (barrel chest)* *From the collection of Manoochehr Abadian Sharifabad, MD* • In contrast to smoking-related COPD, alpha-1 antitrypsin deficiency mainly affects lower fields. • Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend consideration of CT scan for patients with persistent exacerbations, those with symptoms that do not correspond with disease severity on lung function testing, those with	**hyperinflation**

Test	Result
FEV_1 <45% of predicted with significant hyperinflation, and those meeting criteria for lung cancer screening.[1] • Annual low-dose CT scan (LDCT) is recommended by the US Preventive Services Task Force for lung cancer screening in patients with COPD that is due to smoking.[72]	
serial peak flow measurement • May be used to exclude asthma if there is diagnostic uncertainty.[2]	**<20% diurnal or day-to-day variability**
sputum culture • In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum should be sent for culture.[1]	**infecting organism**
alpha-1 antitrypsin level • 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 [<45 years] and nonsmokers).[1] All patients with a diagnosis of COPD should be screened once, especially in areas with high prevalence of alpha-1 antitrypsin deficiency.[70] [71]	**should be normal in patients with COPD that is related to smoking**
exercise testing • Can be of value in patients with a disproportional degree of dyspnea compared with spirometry.[1] 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).[74] Exercise testing is of use in selecting patients for rehabilitation.	**poor exercise performance or exertional hypoxemia is suggestive of advanced disease**
sleep study • Obstructive sleep apnea, a common finding in patients with COPD, is associated with increased risk of death and hospitalization in patients with COPD.[73]	**elevated apnea-hypopnea index and/or nocturnal hypoxemia**
respiratory muscle function • Respiratory muscle function may be tested if dyspnea or hypercapnia are disproportionately increased with respect to FEV_1, as well as in patients with poor nutrition and those with corticosteroid myopathy.[75]	**reduced maximal inspiratory pressure**
ECG • Risk factors for COPD are similar to those for ischemic heart disease, so comorbidity is common. Right-sided heart failure may develop in longstanding COPD (cor pulmonale).	**signs of right ventricular hypertrophy, arrhythmia, ischemia**
echocardiogram • To assess cardiac status if cardiac disease or pulmonary hypertension are suspected.[2]	**may be normal or may show right-sided heart failure and/or pulmonary hypertension**
blood eosinophil count • Blood eosinophil counts can identify patients who are more likely to respond to inhaled corticosteroids (ICS).[76] [77] [78] They may predict the effectiveness of adding ICS to regular long-acting bronchodilator treatment to prevent exacerbations.[77] [78] [79] Little or no effect is seen with ICS at blood eosinophil counts of <100 cells/microliter, while maximal effect is seen at blood eosinophil counts of ≥300 cells/microliter.[76] [80] These thresholds indicate approximate	**may be normal or increased**

Test	Result
cut-off values that may help clinicians predict the likelihood of ICS treatment benefit.[1] Patients with blood eosinophils ≥300 cells/microliter are at greatest risk of exacerbations after withdrawing ICS.[81]	

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Asthma	• 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.	• 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, although may also be present in COPD.
Congestive heart failure	• Usually a history of cardiovascular diseases is present. Patients report symptoms of orthopnea, and fine bibasilar inspiratory crackles may be heard on auscultation.	• B-type natriuretic peptide levels are usually elevated, and chest x-ray reveals increased pulmonary vascular congestion. Transthoracic echocardiogram establishes the structure and function of the left ventricle.
Bronchiectasis	• 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.	• Chest CT reveals bronchial dilation and bronchial wall thickening.
Tuberculosis	• A history of fever, night sweats, weight loss, and chronic productive cough is usually present. Tuberculosis is more common in people living in or originating from endemic areas.	• The diagnosis requires microbiologic confirmation. Infiltrates, fibrosis, or granuloma seen on chest x-ray or chest CT may suggest tuberculosis. Patients usually have positive skin test for tuberculosis.
Bronchiolitis	• Bronchiolitis may affect patients at younger ages. The patient may have a history of connective tissue disorders, especially rheumatoid arthritis, or fume exposure. Some cases are postinfectious.	• 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

Condition	Differentiating signs / symptoms	Differentiating tests
		in children due to radiation risk.
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 visualization of the affected airway by endoscopy.
Chronic rhinosinusitis/ postnasal drip	• Chronic rhinosinusitis is a very common cause of chronic cough. Patients may complain of sinus pressure, rhinorrhea, nonproductive cough, and/or headache.	• Nasal endoscopy, CT of sinuses, and/or empiric trial of antihistamines are commonly utilized to aid in diagnosis.
Gastroesophageal reflux disease (GERD)	• Patients with GERD 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 empiric therapy with proton-pump inhibitors.
ACE inhibitor-induced chronic cough	• ACE inhibitors can cause chronic cough; however, the cough is usually nonproductive.	• Diagnosis is usually based on improvement of symptoms after empiric cessation of ACE inhibitor.
Lung cancer	• Patients may have weight loss, night sweats, hemoptysis, 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 postbronchodilator FEV_1/FVC ratio of <0.7 is commonly considered diagnostic for COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) system categorizes airflow limitation into stages. In patients with FEV_1/FVC <0.7:

- GOLD 1 - mild: FEV_1 ≥80% predicted
- GOLD 2 - moderate: 50% ≤ FEV_1 <80% predicted

- GOLD 3 - severe: 30% ≤ FEV_1 <50% predicted
- GOLD 4 - very severe: FEV_1 <30% predicted.

The GOLD guideline uses a combined "ABE" approach to assess patients according to their level of 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. GOLD cautions against the use of the mMRC dyspnea scale alone for assessing patients, as symptoms of COPD go beyond dyspnea alone. For this reason, the CAT is preferred. However, GOLD acknowledges that the use of the mMRC scale is widespread, and so a threshold of an mMRC grade ≥2 is still included to define "more breathless" patients, as opposed to "less breathless" patients, in its assessment criteria. Exacerbations are assessed independently of symptoms to highlight their clinical relevance.

- Group A: low risk (0-1 exacerbations per year, not requiring hospitalization) and fewer symptoms (mMRC 0-1 or CAT <10)
- Group B: low risk (0-1 exacerbations per year, not requiring hospitalization) and more symptoms (mMRC ≥2 or CAT ≥10)
- Group E: high risk (≥2 exacerbations per year, or ≥1 requiring hospitalization) and any level of symptoms.

Screening

The US Preventive Services Task Force (USPSTF) recommends against screening asymptomatic adults.[82] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines advocate early case-finding by performing spirometry in patients with symptoms and/or risk factors for COPD.[1] Decline in lung function is decreased when COPD is diagnosed at an early stage and risk factors are eliminated.[83]

UK guidelines advise spirometry in all patients ages 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

The 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] Systematic reviews report a modest reduction in rate of decline of FEV_1 among patients receiving pharmacologic therapy.[84] [85] Further research is needed to find out which patients are most likely to benefit.

There is a stepwise approach to therapy, and treatment should be individualized for general health status and comorbid conditions. If a patient with COPD has concomitant asthma, they should primarily be managed according to asthma guidelines.[1] See Asthma in adults . For details on the management of alpha-1 antitrypsin deficiency, see Alpha-1 antitrypsin deficiency .

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

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 wellbeing will improve, and hospital admissions will be significantly decreased, when self- or professional monitoring of disease is being utilized.[86] Such assessment of the medical history should include:

Exposure to risk factors and preventive 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:

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

Comorbidities:

- Assessment of coexisting medical problems (e.g., heart failure) that 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.

One Cochrane review found that integrated disease management (IDM), in which several healthcare providers (physical therapist, pulmonologist, nurse, etc.) work together with patients, probably results in improvement in disease-specific quality of life, exercise capacity, hospital admissions, and hospital days per person.[87] [Evidence A]

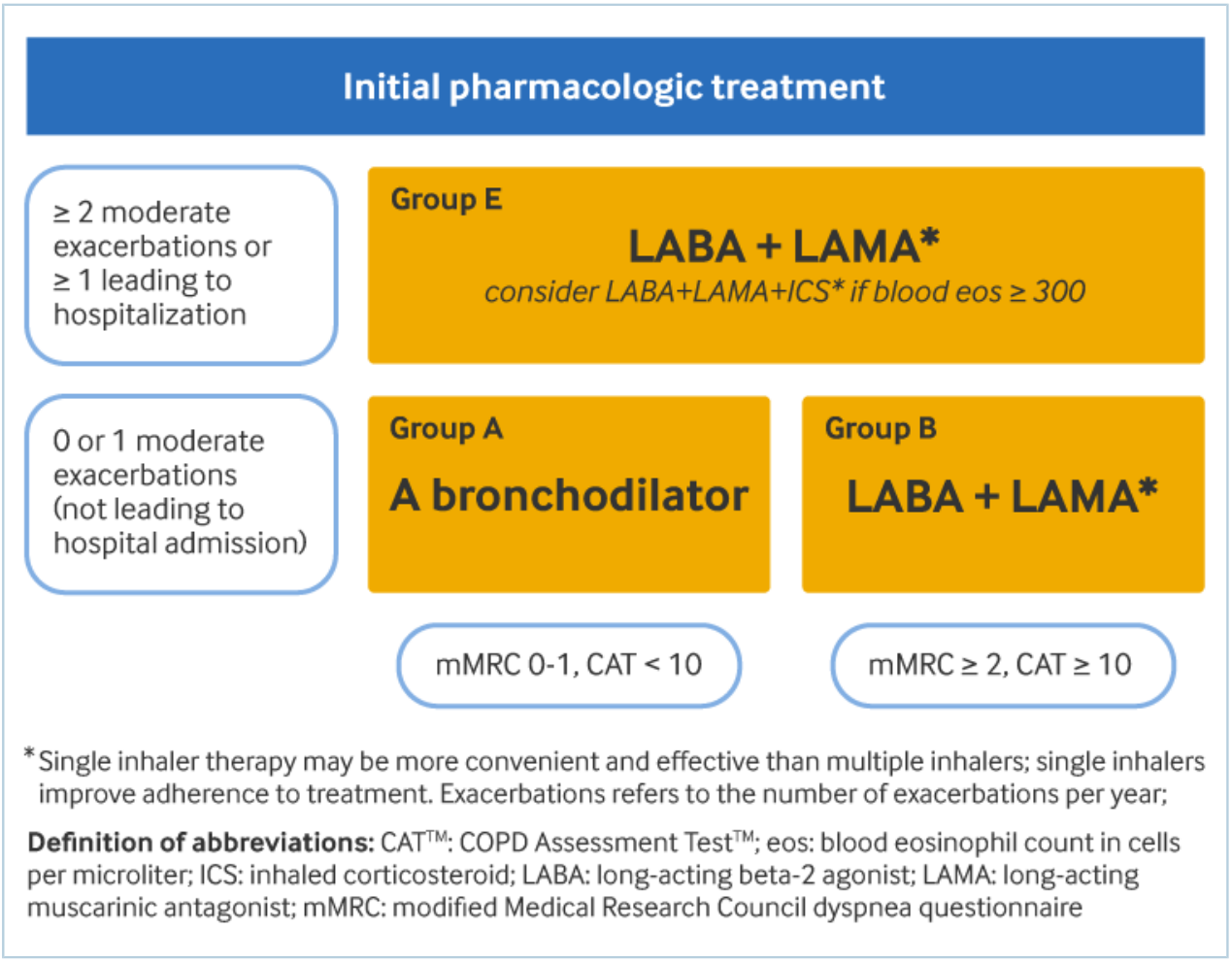
Acute exacerbations

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

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 [Modified British Medical Research Council {mMRC} 0-1 or COPD Assessment Test {CAT} <10] and low risk of exacerbations [0-1 exacerbations per year, not requiring hospitalization]), 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 very occasional dyspnea.
- For group B patients (more symptoms [mMRC ≥2 or CAT ≥10] and low risk of exacerbations [0-1 exacerbations per year, not requiring hospitalization]), LABA/LAMA combination treatment should be offered first-line in the absence of issues with adverse effects or availability. Otherwise, monotherapy with either a LAMA or a LABA may be prescribed. There is no evidence to recommend one class of long-acting bronchodilator over another for bronchodilator monotherapy. The choice should depend on the patient's perception of symptom relief. Patients in group B may have comorbidities that add to their symptoms and impact their prognosis, and so any potential comorbidities should be considered and investigated.
- For group E patients (high risk of exacerbations [≥2 exacerbations per year, or ≥1 requiring hospitalization] and any level of symptoms), LABA/LAMA combination treatment is first-line therapy in the absence of issues with adverse effects or availability. Addition of an inhaled corticosteroid (ICS) to a LABA/LAMA combination may be considered if the patient's blood eosinophil count is ≥300 cells/microliter (triple therapy). Use of ICS with LABA alone is not recommended.



Initial pharmacologic management of COPD

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2025 report); reproduced with permission

Further treatment is determined by the patient's dyspnea/exercise limitation symptom burden and frequency of exacerbations after review and is independent of the patient's GOLD group at diagnosis. GOLD recommends different treatment pathways depending on whether the primary treatment goal is relieving dyspnea/exercise limitation symptoms or reducing exacerbations. If treatment is required for both purposes, clinicians should follow the exacerbation pathway.[1]

Before any adjustment in treatment, patients should be reviewed for symptoms and exacerbation risk, and their inhaler technique and treatment adherence assessed. The role of nonpharmacologic treatment should also be assessed. If the patient's response to initial treatment is appropriate, then the initial treatment can be maintained. Adjustment of pharmacologic 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 adverse effects.[1]

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

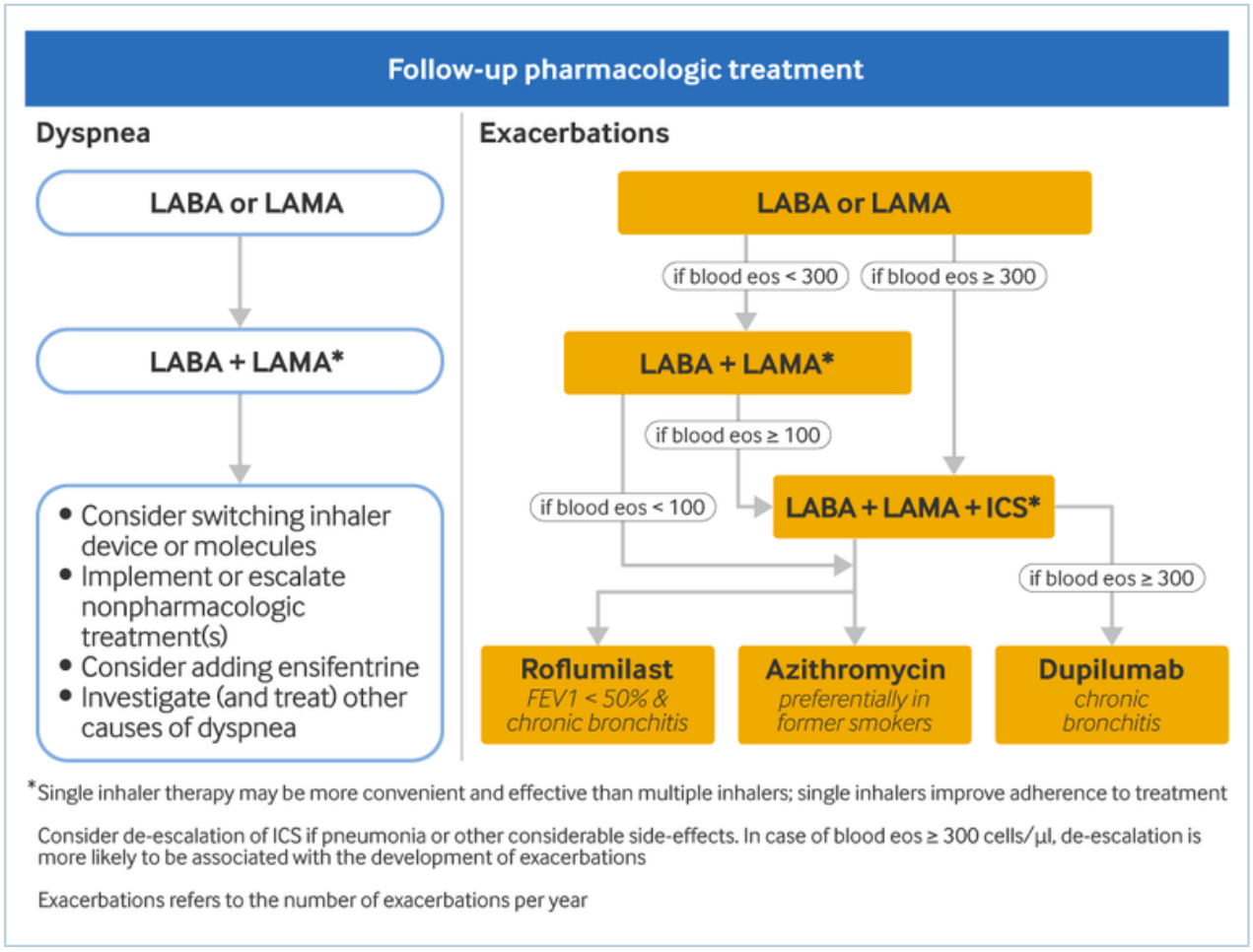
- Patients taking long-acting bronchodilator monotherapy should start a second long-acting bronchodilator

- If symptoms persist following addition of a second long-acting bronchodilator
    - consider switching the inhaler device or molecules
    - implement or escalate nonpharmacologic treatment (e.g., pulmonary rehabilitation)
    - consider adding ensifentrine (a phosphodiesterase-3 [PDE-3] and PDE-4 inhibitor)
- Dyspnea due to other causes should be considered, investigated, and treated. Inhaler technique and adherence should also be reassessed, 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 LABA/LAMA. Blood eosinophil counts can identify patients who are more likely to respond to ICS.[76] [77] [78] Escalation to triple therapy with LABA/LAMA/ICS may be considered for patients on long-acting bronchodilator monotherapy if their peripheral eosinophil count is ≥300 cells/microliter. ICS is unlikely to be beneficial in patients whose blood eosinophil count is <100 cells/microliter.
- Patients who take LABA/LAMA and whose blood eosinophils are ≥100 cells/microliter 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 hospitalization.[80] [88] [89] [90] [91] [92] [93] [94][95] American Thoracic Society guidelines recommend the use of triple therapy in patients who have had one or more exacerbations requiring oral corticosteroids, antibiotics, or hospitalization in the past year and who have symptoms of dyspnea or reduced exercise tolerance despite LABA/LAMA dual therapy.[96] UK guidelines recommend the use of triple therapy in patients who have an exacerbation requiring hospitalization, 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/microliter should add roflumilast or azithromycin.
- LABA/ICS is not recommended by GOLD. However, a patient with COPD who previously had exacerbations that responded to LABA/ICS (and has no current exacerbations) may continue on LABA/ICS; high symptom load may merit escalation to LABA/LAMA/ICS in this patient population. If a patient currently receiving LABA/ICS has no relevant exacerbation history, consider switching to LABA/LAMA. Patients on LABA/ICS with current exacerbations and blood eosinophil count <100 cells/microliter may be candidates for changing to LABA/LAMA. Those with current exacerbations and blood eosinophil count ≥100 cells/microliter while using LABA/ICS should be escalated to triple therapy by addition of a LAMA.
- Patients who take LABA/LAMA/ICS may add roflumilast, azithromycin, or dupilumab (an interleukin [IL]-4 receptor antagonist monoclonal antibody). Roflumilast may be considered in patients with forced expiratory volume in 1 second (FEV_1) <50% predicted and chronic bronchitis, particularly if they have had at least one hospitalization for an exacerbation in the last year. The risk of developing antibiotic-resistant organisms should be considered when prescribing azithromycin. Dupilumab may be considered in patients with chronic bronchitis whose blood eosinophil count is ≥300 cells/microliter. ICS can be discontinued if it is ineffective or causing adverse effects. Patients with blood eosinophils ≥300 cells/microliter are at greatest risk of exacerbations after withdrawing ICS.[81]

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



Escalation therapy for patients with COPD. Definition of abbreviations: ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2025 report); reproduced with permission

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., albuterol, levalbuterol) 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.[97] 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 dyspnea.[1] [98] However, regular use of short-acting bronchodilators is not generally recommended.[1]

Tiotropium, a LAMA, has been shown to reduce risk of exacerbation versus placebo or other maintenance treatments.[99] Newer LAMAs, such as aclidinium, glycopyrrolate, and umeclidinium, have at least comparable efficacy to tiotropium, in terms of change from baseline in trough FEV_1, transitional dyspnea

index focal score, St George's Respiratory Questionnaire score, and rescue medication use.[100] Revefenacin is a nebulized 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.[101] [102] One study concluded that aclidinium was not associated with an increase in major adverse cardiovascular events, compared with placebo.[103] A population-based cohort study found that older men with COPD newly started on LAMAs are at increased risk of urinary tract infections.[104]

LABAs and LAMAs both significantly improve lung function, dyspnea, and health status and reduce exacerbation rates. [Evidence A] In cases of stable COPD, if the decision is made to use single-agent therapy, LAMA may be superior to LABA agents.[105] LAMAs have a greater effect on exacerbation reduction than LABAs in patients with moderate to very severe COPD.[106] [107] The long-term safety of LAMA was demonstrated in the UPLIFT trial.[108]

A LABA/LAMA combination may provide a better therapeutic effect without increasing the adverse effects of each class.[105] [109] [110] [111] [112] Umeclidinium/vilanterol, glycopyrrolate/formoterol, tiotropium/olodaterol, and aclidinium/formoterol are approved for use in COPD. Systematic reviews and meta-analyses have found that combination therapy with a LABA/LAMA:

- reduces exacerbation rate compared with monotherapy
- is associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild/moderate COPD, compared with placebo;[113]
- improves FEV_1 and modestly reduces risk of pneumonia in patients with stable chronic obstructive pulmonary disease, but increases odds of all-cause death from 1% to 1.4%.[114]

Umeclidinium/vilanterol decreases the risk of exacerbations in patients with mild/moderate COPD.[113] One systematic review and network meta-analysis found that all LABA/LAMA fixed-dose combinations had a similar efficacy and safety.[115]

As outlined above, GOLD makes recommendations on the initial agent based on the patient's risk group (A, B, or E).[1] American Thoracic Society guidelines recommend initiating LABA/LAMA dual therapy in preference to monotherapy in patients with COPD who have dyspnea or exercise intolerance.[96] UK guidelines recommend initiating dual therapy with a LABA/LAMA or LABA/ICS if a patient has symptoms or exacerbations despite nonpharmacologic 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.[2]

Inhaled corticosteroids (ICS)

When indicated in patients with COPD, ICS should always be prescribed in combination with long-acting bronchodilators. ICS are believed to be effective because of their anti-inflammatory effects. Long-term ICS use reduces the need to use rescue therapy and reduces exacerbations, and may also decrease mortality.[116] [117] [118]

The effect of treatment regimens containing ICS is higher in patients at higher risk of exacerbations (two or more exacerbations and/or one hospitalization for an exacerbation in the previous year).[90] [92] [119] Blood eosinophil count may predict the effectiveness of adding ICS to regular long-acting bronchodilator treatment to prevent exacerbations.[77] [78] [79] Little or no effect is seen at blood eosinophil counts of <100 cells/microliter, while maximal effect is seen at blood eosinophil counts of ≥300 cells/microliter.[76] [80] These thresholds indicate approximate cut-off values that may help clinicians predict the likelihood of a treatment benefit.[1] Former smokers are more corticosteroid-responsive than current smokers at any

eosinophil count.[79] 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.[92] [120] Short-term ICS use (≤1 year) may be associated with greater improvements in FEV_1 than long-term use, although further studies are needed to better understand the effect of treatment on lung function.[121]

Several studies have pointed to an increased risk of pneumonia in patients with COPD taking ICS.[85] This risk is higher for fluticasone in comparison with budesonide.[122] [123] [124] A study in a large cohort of Danish patients found the risk of acquiring *Pseudomonas aeruginosa* , a common cause of hospital-acquired pneumonia, to be dose-dependent, with high-dose ICS associated with the greatest risk. The study also found that patients with *P aeruginosa* were more likely to have a lower BMI and FEV_1 than *P aeruginosa* -negative patients.[125] One systematic review and meta-analysis found that, despite a significant increase in unadjusted risk of pneumonia associated with use of ICS, pneumonia fatality and overall mortality were not increased in randomized controlled trials and were decreased in observational studies.[126] Therefore, an individualized treatment approach that assesses a patient's risk of pneumonia versus the benefit of decreased exacerbations should be implemented.[85] [127] [128] Concern is also raised with regards to increased risk of tuberculosis and influenza in adult patients with COPD who are on ICS therapy, although one meta-analysis found that less than 1% of all assessed tuberculosis cases were attributable to ICS exposure.[129] [130] ICS may also cause oropharyngeal candidiasis and hoarseness.[85]

Although there have been reports of ICS use either increasing or decreasing the risk of lung cancer, the available data do not appear to support either conclusion; further studies are needed.[1]

Clinicians should weigh the potential benefits and risks of prescribing ICS and discuss these with the patient.[2] A history of hospitalization(s) for exacerbations of COPD, two or more moderate exacerbations per year despite regular long-acting bronchodilators, blood eosinophils of ≥300 cells/microliter, and/or previous or concomitant asthma all strongly favor initiating ICS.[131] Repeated episodes of pneumonia, blood eosinophils <100 cells/microliter, and/or history of mycobacterial infection are all factors against the use of ICS.[131] 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/microliter.[131]

The European Respiratory Society has produced a guideline on the withdrawal of inhaled corticosteroids in COPD.[132]

Long-term use of oral corticosteroids in COPD is not recommended.[96] 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.[2]

Combined bronchodilator and corticosteroid preparations

A combination preparation of a long-acting bronchodilator and an ICS may be used for patients who require both these agents. This is convenient and may help with compliance in some patients. The choice of therapy in this class is based on availability and individual response and preference.[133] 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 hospitalization.[80] [88] [89] [90] [91] [92] [93] [94][95] 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.[134] One randomized controlled trial has reported a reduction in all-cause mortality in patients with FEV_1 <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.[135] Another randomized controlled trial had similar findings in terms of mortality in the triple therapy arm (budesonide/glycopyrrolate/formoterol), but only at the higher dose of ICS.[95] [136] 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.[95] For both studies, there were no differences in mortality compared with LABA/ICS.[95] [135] [136] 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 nonsignificant trend for lower mortality with triple therapy compared with non-ICS treatments.[137] These results are strengthened by findings from a meta-analysis of over 200 studies: triple therapy provided a significant reduction in mortality versus dual therapy, although was associated with greater risk of pneumonia. No differences were observed between regimens in lung function or health-related quality of life.[138]

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.[2] The ICS may be withdrawn if the patient has had no exacerbations in the past year.[96] One systematic review of data from real-world studies found little to no evidence of worsened outcomes when ICS was withdrawn and followed by appropriate pharmacologic management in patients with moderate to severe COPD.[139]

Phosphodiesterase inhibitors

Roflumilast is an oral phosphodiesterase (PDE)-4 inhibitor that inhibits the breakdown of cAMP. It may be considered in patients with FEV_1 <50% predicted and chronic bronchitis who are taking LABA/LAMA/ICS, particularly if they have had at least one hospitalization 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.[140]

Ensifentrine is a selective PDE-3 and PDE-4 inhibitor approved in the US for the maintenance treatment of COPD in adults. It combines bronchodilator and nonsteroidal anti-inflammatory effects within a single molecule. Ensifentrine may be considered as an add-on bronchodilator for patients with stable COPD taking LABA/LAMA who have persistent dyspnea symptoms.[1] Clinical benefits were apparent when used as monotherapy and with other maintenance therapies.[141] Nonetheless, enfensitrine's place in therapy requires further study.

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.[142] [143] [144] [145] One Cochrane review ranked macrolides first in reducing exacerbations and serious adverse events, and improving quality of life, above fluoroquinolones and tetracyclines.[145] 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.[146] 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.[147] Azithromycin increases the risk of colonization with macrolide-resistant organisms and should not be prescribed for patients with hearing impairment, resting tachycardia, or apparent risk of QTc prolongation.[148] Azithromycin should be considered preferentially, but not only, in former smokers with persistent exacerbations despite appropriate therapy.[1]

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 hospitalization per year.[149] 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 optimized, and bronchiectasis should be excluded with a CT scan.[2] [149] ECG and liver tests should be repeated after 1 month of treatment. A head-to-head comparison of fluoroquinolones, tetracyclines, and macrolides given for 12-13 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.[150]

Prophylactic antibiotic therapy should be reviewed at 6 and 12 months to determine whether there is a benefit in terms of exacerbation rates.[149] If antibiotic therapy is not effective it should be stopped.

Biologic therapies

Dupilumab, an IL-4 receptor antagonist, may be considered for patients with moderate to severe COPD taking LABA/LAMA/ICS with a history of exacerbations, chronic bronchitis, and blood eosinophils ≥300 cells/microliter.[1] [151] [152] Dupilumab should not be used for relief of acute bronchospasm. Dupilumab is approved in the US and Europe for add-on maintenance treatment in adults with uncontrolled COPD characterized by elevated blood eosinophils.

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 has modest effects on lung function in moderate to severe COPD.[153] A large randomized controlled trial found no effect of oral theophylline alone or with prednisone on exacerbations of severe COPD.[154] Experts may prescribe theophylline after a patient has exhausted all options for inhaled therapies. Theophylline is not recommended unless other long-term bronchodilators are unavailable or unaffordable.[1]

Patient education and self-management

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

One Cochrane review found that self-management interventions that include an action plan for acute exacerbations of COPD are associated with improvements in health-related quality of life and fewer admissions to the hospital for respiratory problems. An exploratory analysis found a small, but significantly higher, respiratory-related mortality rate for self-management compared to usual care, although no excess risk of all-cause mortality was seen.[155] A randomized controlled trial showed that a 3-month program of self-management started in patients with COPD exacerbations recently discharged from the hospital led to increases in COPD-related hospitalizations and emergency department visits over 6 months.[156]

Self-management plans should include personalized 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. It is estimated that patients with COPD are 1.9 times more likely to die from suicide than those without COPD, and symptoms of anxiety, depression, and frustration are common.[157] [158] Studies have found a beneficial effect of cognitive behavioral therapy (CBT) on outcomes including symptoms of depression and anxiety, quality of life, and frequency of emergency department visits.[159] [160] [161] Further research is warranted into the effects of high-resource-intensive versus low-resource-intensive CBT.[161]

One randomized controlled trial found that a telephone health coaching intervention to promote behavior change in patients with mild COPD in primary care led to improvements in self-management activities, but did not improve health-related quality of life.[162] 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.[163]

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.[164] [165] Poor technique is more likely when patients are using multiple devices or have never received inhaler technique training.[166] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[167] Demonstration using a placebo device may be most effective for teaching inhaler technique to adults ages ≥65 years.[168] 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.[169] [170] Inhaler device attributes such as rapid onset of symptom relief and small size have been recorded in patient preference studies.[171] [172]

Physical activity is recommended for all patients with COPD.[1] One systematic review and meta-analysis of randomized controlled trials found that exercise training on its own can improve physical activity in COPD, and greater improvements can be made with the addition of physical activity counseling.[173] 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.[174] Other studies have demonstrated improvements in peak oxygen uptake, perceived fatigue, and health-related quality of life following adherence to supervised and unsupervised exercise programs.[175] [176] [177] One Cochrane review found limited evidence for improvement in physical activity with physical activity counseling, exercise training, and pharmacologic management of COPD.

The authors commented that assessment of quality had been limited by lack of methodologic detail and the diverse range of interventions had primarily been assessed in single studies.[178] The optimal timing, components, duration, and models for improving physical activity remain unclear. Meta-analyses suggest that yoga, Qigong, and other home-based breathing exercises can improve exercise capacity and pulmonary function in patients with COPD.[179] [180] [181] Tai Chi has been shown to improve exercise capacity compared with usual care.[182]

Dietary advice and oral supplements have been found to improve body weight, quality of life, respiratory muscle strength, and 6-minute walk distance.[183] [184] However, nutritional support has not been consistently found to improve lung function.[184]

Smoking cessation

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 programs include counseling, group meetings, and drug therapy.[185] Some patients may need frequent referrals to achieve success. Smoking cessation that includes pharmacotherapy and intensive counseling has a higher success rate and is cost effective in COPD, with low costs per quality-adjusted life year.[186] [187] [188]

The use of electronic nicotine delivery systems (ENDS), including e-cigarette and vaping products, as tobacco cessation aids is controversial. Evidence from observational studies does not currently support the use of ENDS as an aid to smoking cessation in people with COPD.[189] See Smoking cessation (Management approach) .

Mucolytics

Patients with the chronic bronchitis phenotype of COPD often produce thick sputum on a frequent basis. Mucolytic agents (erdosteine, carbocysteine, and acetylcysteine) 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.[190] [191] [192] Erdosteine and carbocysteine are not available in the US. Treatment with mucolytic agents such as carbocysteine and acetylcysteine may reduce exacerbations and modestly improve health status in patients not receiving ICS.[1] However, erdosteine may have a significant effect on mild exacerbations whether or not the patient is taking ICS.[1]

Pulmonary rehabilitation

Pulmonary rehabilitation comprises 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.[1] [193] [194] GOLD guidelines recommend pulmonary rehabilitation for patients with high symptom burden and risk of exacerbation (i.e., groups B and E).[1]

Pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.[195] 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. There is evidence to support starting pulmonary rehabilitation within 1 month of an acute exacerbation.[196] [197]

A large US cohort study found that initiation of pulmonary rehabilitation within 90 days of hospital discharge was significantly associated with lower mortality risk at 1 year and fewer rehospitalizations at 1 year.[198] [199] Less than 2% of the patient cohort initiated rehabilitation within this timeframe, highlighting the need to develop more effective strategies to encourage patient participation.[198] However, starting pulmonary rehabilitation before hospital discharge could be associated with a higher 12-month mortality, so is not recommended.[200]

Pulmonary rehabilitation also decreases the depression and anxiety related to COPD, and reduces hospitalization.[201]

The benefit of pulmonary rehabilitation appears to subside after termination of the course unless patients follow a home exercise schedule.[202] Maintenance pulmonary rehabilitation, defined as ongoing supervised exercise at a lower frequency than the original rehabilitation program, may have a role in preserving the benefits of pulmonary rehabilitation over time. Findings from one Cochrane review indicate that supervised maintenance programs may improve health-related quality of life and exercise capacity at 6-12 months compared with usual care.[203]

Benefits of home- or community-based pulmonary rehabilitation on respiratory symptoms and quality of life in patients with COPD can match those of the hospital-based rehabilitation programs.[204] [205] [206] One Cochrane review concluded that both primary and maintenance telerehabilitation achieved similar outcomes to in-person rehabilitation with no safety issues. Limitations of the review include small patient numbers and heterogeneity in telerehabilitation models.[207]

Oxygen therapy and ventilatory support

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

- PaO_2 ≤7.3 kPa (55 mmHg) or SaO_2 ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or
- PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).

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 hypoxemia. The ATS defines severe hypoxemia as either:[208]

- PaO_2 ≤7.3 kPa (55 mmHg) or oxygen saturation as measured by pulse oximetry (SpO_2) ≤88%; or
- PaO_2 7.5 to 7.9 kPa (56-59 mmHg) or SpO_2 of 89% plus one of the following: edema, hematocrit ≥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.[208]

Supplemental oxygen should be titrated to achieve SaO_2 ≥90%.[1] 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 minimize pulmonary hypertension by decreasing pulmonary artery pressure, and improves exercise tolerance and quality of life. It has been shown to improve survival.[1] [66]

There is some evidence that oxygen can relieve breathlessness when given during exercise to mildly hypoxemic and nonhypoxemic people with COPD who do not otherwise qualify for home oxygen therapy.[209] 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 hypoxemia.[208] However, the ATS suggests not prescribing long-term oxygen therapy in adults with COPD who have moderate chronic resting room air hypoxemia (SpO_2 of 89% to 93%).[208]

Air travel is safe for most patients receiving long-term oxygen therapy, although patients should be able to tolerate short periods without oxygen as it is likely there will be times it is unavailable.[1] [210] Patients with SaO_2 >95% at sea level and SaO_2 ≥84% after a 6-minute walk test may travel by air without further assessment.[1] [210] [211] Supplemental oxygen is recommended for patients with SaO_2 92% to 95% at sea level and SaO_2 <84% after a 6-minute walk test, and for patients with SaO_2 <92% at sea level.[211] Hypoxia-altitude simulation testing (also known as hypoxic challenge testing) should be performed for other patients.[210] [211] For patients on long-term oxygen therapy, the British Thoracic Society recommends considering in-flight oxygen at 2L/minute more than the patient's usual prescription.[210]

For patients who have COPD and obstructive sleep apnea, ventilatory support with continuous positive airway pressure (CPAP) can improve survival and reduce hospital admissions.[1] [73] Noninvasive ventilation (NIV) is occasionally used in patients with very severe but stable COPD, although the optimal timing for initiation and best selection criteria for candidates is unclear.[1] [212] [213] One Cochrane review found that chronic NIV delivered via a facial mask improved survival and conferred short-term health-related quality of life benefit in stable COPD. Chronic NIV also improved duration of hospital admission-free survival in patients with persistent hypercapnia following an exacerbation.[213] Another study reported a significant decrease in exacerbation frequency with NIV versus control therapy, although no improvements were observed in mortality, PaO_2, $PaCO_2$, or pH.[214]

Guidelines from the ATS suggest the use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD.[215] The European Respiratory Society and Canadian Thoracic Society have issued similar guidance.[216] [217]

Surgery

Surgical interventions are the last step in the management of COPD, and include bullectomy, lung volume reduction surgery, and lung transplant.[218] [219] They are used to improve lung dynamics, exercise adherence, and quality of life.[219] Lung volume reduction surgery is indicated in patients with very severe airflow limitation, and especially in patients with localized upper lobe disease and lower than normal exercise capacity.[218] One meta-analysis found an increased risk of early mortality in patients who underwent lung volume reduction surgery compared to standard care; however, no significant difference was observed in overall mortality.[220] Bullectomy is an option in COPD patients with dyspnea in whom CT reveals huge bullae occupying at least 30% of the hemithorax. Severely poor functional status and severe decrease in FEV_1 (<500 mL) make these options less favorable. Endobronchial valve insertion can produce clinically meaningful improvements in appropriately selected patients with COPD.[220] [221] [222] The procedure may be most beneficial in patients whose dyspnea is primarily due to hyperinflation and air trapping in the air spaces distal to the terminal bronchioles, which manifests as

emphysema with markedly increased residual volume. Contraindications include active lung infection and incomplete lobar fissures (<80%).[223] The most common adverse events associated with endobronchial valve insertion are pneumothorax and exacerbation.[220]

Criteria for referral for lung transplantation include:[224]

- Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) score 5-6 with additional factor(s) present suggestive of increased risk of mortality:
    - Frequent acute exacerbations
    - Increase in BODE score >1 over past 24 months
    - Pulmonary artery to aorta diameter >1 on CT scan
    - FEV_1 20% to 25% predicted
- Clinical deterioration despite maximal treatment including medication, pulmonary rehabilitation, oxygen therapy, and, as appropriate, nocturnal noninvasive positive pressure ventilation
- Poor quality of life unacceptable to the patient
- For a patient who is a candidate for bronchoscopic or surgical lung volume reduction (LVR), simultaneous referral for both lung transplant and LVR evaluation is appropriate

Lung transplantation has been shown to improve quality of life and functional capacity.[219] However, lung transplantation does not appear to confer a survival benefit.[225]

Palliative care

Palliative therapies to improve symptoms of dyspnea, offer nutritional support, address anxiety and depression, and reduce fatigue may benefit patients with COPD who experience these despite optimal medical therapy. 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.[1] [226] Opioid analgesics, fans, neuromuscular electrical stimulation, and chest wall vibration can relieve dyspnea.[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.[227] Another study found that regular, low-dose, oral sustained-release morphine for 4 weeks improved disease-specific health status in patients with COPD and refractory breathlessness.[228]

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.[229]

Acupuncture and acupressure may also improve breathlessness and quality of life in patients with advanced COPD.[230]

Treatment algorithm overview

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

Acute (summary)		
GOLD group A: initial treatment		
	1st	short- or long-acting bronchodilator
	plus	supportive care and advice
GOLD group B: initial treatment		
	1st	LABA/LAMA
	plus	short-acting bronchodilator
	plus	supportive care and advice
	plus	pulmonary rehabilitation
	2nd	LABA or LAMA
	plus	short-acting bronchodilator
	plus	supportive care and advice
	plus	pulmonary rehabilitation
GOLD group E: initial treatment		
	1st	LABA/LAMA or LABA/LAMA/ICS
	plus	short-acting bronchodilator
	plus	supportive care and advice
	plus	pulmonary rehabilitation

Ongoing		(summary)
GOLD group A, B, or E: persistent dyspnea/exercise limitation after initial therapy		
	1st	LABA/LAMA
	plus	short-acting bronchodilator
	plus	supportive care and advice
	adjunct	pulmonary rehabilitation
	adjunct	oxygen therapy and/or ventilatory support
	adjunct	ensifentrine
	adjunct	mucolytic
	adjunct	theophylline
	adjunct	bronchoscopic intervention or surgery
	adjunct	palliative care
GOLD group A, B, or E: persistent exacerbations after initial therapy		
	1st	LABA/LAMA or LABA/LAMA/ICS
	plus	short-acting bronchodilator
	plus	supportive care and advice
	adjunct	pulmonary rehabilitation
	adjunct	oxygen therapy and/or ventilatory support
	adjunct	roflumilast
	adjunct	azithromycin
	adjunct	dupilumab
	adjunct	mucolytic
	adjunct	theophylline
	adjunct	bronchoscopic intervention or surgery
	adjunct	palliative care

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

GOLD group A: initial treatment

1st **short- or long-acting bronchodilator**

Primary options

SABA

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

OR

SABA

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

OR

SAMA

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

OR

LABA

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

OR

LABA

» arformoterol inhaled: 15 micrograms nebulized 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

Acute

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

» glycopyrrolate inhaled: (25 micrograms/vial nebulizer inhalation solution) 25 micrograms nebulized twice daily using Magnair® nebulizer device

» Global Initiative for Chronic Obstructive Lung Disease (GOLD) group A patients are characterized by few symptoms (Modified British Medical Research Council [mMRC] 0-1 or COPD Assessment Test [CAT] <10) and low risk of exacerbations (0-1 exacerbations per year, not requiring hospitalization).[1]

» 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 very occasional dyspnea.[1] LABAs and LAMAs both significantly improve lung function, dyspnea, and health status and reduce exacerbation rates. [Evidence A] LAMAs have a greater effect on exacerbation reduction than LABAs.[106] [107]

» 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.[97]

Acute

» SAMAs should be discontinued if a LAMA is prescribed.

» SABAs include albuterol and levalbuterol. Ipratropium is a SAMA. LABAs include salmeterol, arformoterol, and olodaterol. LAMAs include tiotropium, umeclidinium, aclidinium, and glycopyrrolate.

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. See Smoking cessation .

» Depending on local guidelines, patients should be vaccinated against influenza virus, *Streptococcus pneumoniae* , pertussis (whooping cough), varicella-zoster virus (shingles), respiratory syncytial virus, and coronavirus disease 2019 (COVID-19).[1] [231] Vaccination against influenza is associated with fewer exacerbations of COPD.[232] [233]

» 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.[164] [165] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[167]

» 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 medication has been shown to modify the long-term decline in lung function, and the primary goal of pharmacotherapy is to control symptoms and prevent complications. 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/LAMA**

Primary options

LABA/LAMA

Acute

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

OR

LABA/LAMA

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

OR

LABA/LAMA

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

OR

LABA/LAMA

» aclidinium bromide/formoterol inhaled: (400/12 micrograms/dose inhaler) 1 puff twice daily

» Global Initiative for Chronic Obstructive Lung Disease (GOLD) group B patients are characterized by more symptoms (Modified British Medical Research Council [mMRC] ≥2 or COPD Assessment Test [CAT] ≥10) and low risk of exacerbations (0-1 exacerbations per year, not requiring hospitalization).[1]

» Long-acting muscarinic antagonist (LAMA)/long-acting beta-2 agonist (LABA) combination treatment should be offered first-line in the absence of issues with adverse effects or availability.[1]

» Umeclidinium/vilanterol, glycopyrrolate/formoterol, tiotropium/olodaterol, and aclidinium/formoterol are LABA/LAMA combinations approved for use in COPD.[119] [234]
Umeclidinium/vilanterol decreases the risk of exacerbations in patients with mild/moderate COPD.[113]

plus **short-acting bronchodilator**

Treatment recommended for ALL patients in selected patient group

Primary options

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

OR

MANAGEMENT

Acute

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

OR

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

» 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.[97] SAMAs should be discontinued if a long-acting muscarinic antagonist (LAMA) is prescribed. SABAs include albuterol and levalbuterol.

» 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. See Smoking cessation .

» Depending on local guidelines, patients should be vaccinated against influenza virus, *Streptococcus pneumoniae* , pertussis (whooping cough), varicella-zoster virus (shingles), respiratory syncytial virus, and coronavirus disease 2019 (COVID-19).[1] [231] Vaccination against influenza is associated with fewer exacerbations of COPD.[232] [233]

» 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.[164] [165] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at

Acute

subsequent appointments can improve inhaler technique.[167]

» 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 medication has been shown to modify the long-term decline in lung function, and the primary goal of pharmacotherapy is to control symptoms and prevent complications. 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 comprises aerobic exercise, strength training, and education, and should be started early in the disease course.[1] [193] [194] GOLD guidelines recommend pulmonary rehabilitation for patient groups B and E.[1]

» Pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.[195]

» A large US cohort study found that initiation of pulmonary rehabilitation within 90 days of hospital discharge following an acute exacerbation of COPD was significantly associated with lower mortality risk at 1 year and fewer rehospitalizations at 1 year.[198] [199] However, starting pulmonary rehabilitation before hospital discharge could be associated with a higher 12-month mortality, so is not recommended.[200]

2nd **LABA or LAMA**

Primary options

LABA

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

OR

LABA

» arformoterol inhaled: 15 micrograms nebulized twice daily

OR

Acute

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

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

» glycopyrrolate inhaled: (25 micrograms/vial nebulizer inhalation solution) 25 micrograms nebulized twice daily using Magnair® nebulizer device

OR

LAMA

» revefenacin inhaled: 175 micrograms nebulized once daily

» Global Initiative for Chronic Obstructive Lung Disease (GOLD) group B patients are characterized by more symptoms (Modified British Medical Research Council [mMRC] ≥2 or COPD Assessment Test [CAT] ≥10) and low risk of exacerbations (0-1 exacerbations per year, not requiring hospitalization).[1]

» If there are issues with adverse effects or availability, monotherapy with either a LAMA or a LABA may be prescribed.[1] 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

Acute

depend on the patient's perception of symptom relief.[1]

» LABAs and LAMAs both significantly improve lung function, dyspnea, and health status and reduce exacerbation rates.

» LABAs include salmeterol, arformoterol, and olodaterol. LAMAs include tiotropium, umeclidinium, aclidinium, and glycopyrrolate. Revefenacin is a nebulized 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

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

OR

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

OR

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

» 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.[97] SAMAs should be discontinued if a LAMA is prescribed. SABAs include albuterol and levalbuterol.

» 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

Acute

» 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. See Smoking cessation .

» Depending on local guidelines, patients should be vaccinated against influenza virus, *Streptococcus pneumoniae* , pertussis (whooping cough), varicella-zoster virus (shingles), respiratory syncytial virus and coronavirus disease 2019 (COVID-19).[1] [231] Vaccination against influenza is associated with fewer exacerbations of COPD.[232] [233]

» 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.[164] [165] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[167]

» 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 medication has been shown to modify the long-term decline in lung function, and the primary goal of pharmacotherapy is to control symptoms and prevent complications. 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 comprises aerobic exercise, strength training, and education, and should be started early in the disease course.[1] [193] [194] GOLD guidelines recommend pulmonary rehabilitation for patient groups B and E.[1]

» Pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.[195]

» A large US cohort study found that initiation of pulmonary rehabilitation within 90 days

Acute

of hospital discharge following an acute exacerbation of COPD was significantly associated with lower mortality risk at 1 year and fewer rehospitalizations at 1 year.[198] [199] However, starting pulmonary rehabilitation before hospital discharge could be associated with a higher 12-month mortality, so is not recommended.[200]

GOLD group E: initial treatment

1st **LABA/LAMA or LABA/LAMA/ICS**

Primary options

LABA/LAMA

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

OR

LABA/LAMA

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

OR

LABA/LAMA

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

OR

LABA/LAMA

» aclidinium bromide/formoterol inhaled: (400/12 micrograms/dose inhaler) 1 puff twice daily

Secondary options

LABA/LAMA/ICS

» fluticasone furoate/umeclidinium/vilanterol inhaled: (100/62.5/25 micrograms/dose inhaler) 1 puff once daily

OR

LABA/LAMA/ICS

» fluticasone furoate/vilanterol inhaled: (100/25 micrograms/dose inhaler) 1 puff once daily
-or-
» fluticasone propionate/salmeterol inhaled: (250/50 micrograms/dose inhaler) 1 puff twice daily
-or-

Acute

» 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-
» glycopyrrolate inhaled: (25 micrograms/vial nebulizer inhalation solution) 25 micrograms nebulized twice daily using Magnair® nebulizer device

» Global Initiative for Chronic Obstructive Lung Disease (GOLD) group E patients are characterized by a high risk of exacerbations (≥2 exacerbations per year, or ≥1 requiring hospitalization) and any level of symptoms.[1]

» GOLD recommends starting therapy with a long-acting beta-2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) combination.[1]

» Addition of an inhaled corticosteroid (ICS) to a LABA/LAMA combination should be considered if the patient's blood eosinophil count is ≥300 cells/microliter.[1] The effect of treatment regimens containing ICS is higher in patients at higher risk of exacerbations (two or more exacerbations and/or one hospitalization for an exacerbation in the previous year).[90] [92] [119] Blood eosinophil count may predict the effectiveness of adding inhaled corticosteroids to regular long-acting bronchodilator treatment to prevent exacerbations.[77] [78] [79] Little or no effect is seen at blood eosinophil counts of <100 cells/microliter, while maximal effect is seen at blood eosinophil counts of ≥300 cells/microliter.[76] [80] These thresholds indicate approximate cut-off values that 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.[134] Former

Acute

smokers are more corticosteroid-responsive than current smokers at any eosinophil count.[79] 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.[92] [120]

» 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.

» Umeclidinium/vilanterol, glycopyrrolate/formoterol, tiotropium/olodaterol, and aclidinium/formoterol are LABA/LAMA combinations approved for use in COPD.[119] [234] Umeclidinium/vilanterol decreases the risk of exacerbations in patients with mild/moderate COPD.[113]

» Fluticasone/umeclidinium/vilanterol (a LABA/LAMA/ICS combination) is available as a proprietary combination inhaler.

plus **short-acting bronchodilator**

Treatment recommended for ALL patients in selected patient group

Primary options

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

OR

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

OR

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

» 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.[97]

» Ipratropium, a SAMA, may have a small benefit over SABAs in improving health-related quality of life.[97] SAMAs should be discontinued if

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a long-acting muscarinic antagonist (LAMA) is prescribed. SABAs include albuterol and levalbuterol.

» 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. See Smoking cessation .

» Depending on local guidelines, patients should be vaccinated against influenza virus, *Streptococcus pneumoniae* , pertussis (whooping cough), varicella-zoster virus (shingles), respiratory syncytial virus, and coronavirus disease 2019 (COVID-19).[1] [231] Vaccination against influenza is associated with fewer exacerbations of COPD.[232] [233]

» 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.[164] [165] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[167]

» 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 medication has been shown to modify the long-term decline in lung function, and the primary goal of pharmacotherapy is to control symptoms and prevent complications. 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

Acute

» Pulmonary rehabilitation comprises aerobic exercise, strength training, and education, and should be started early in the disease course.[1] [193] [194] GOLD guidelines recommend pulmonary rehabilitation for patient groups B and E.[1]

» Pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.[195]

» A large US cohort study found that initiation of pulmonary rehabilitation within 90 days of hospital discharge following an acute exacerbation of COPD was significantly associated with lower mortality risk at 1 year and fewer rehospitalizations at 1 year.[198] [199] However, starting pulmonary rehabilitation before hospital discharge could be associated with a higher 12-month mortality, so is not recommended.[200]

Ongoing

GOLD group A, B, or E: persistent dyspnea/exercise limitation after initial therapy

1st **LABA/LAMA**

Primary options

LABA/LAMA

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

OR

LABA/LAMA

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

OR

LABA/LAMA

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

OR

LABA/LAMA

» aclidinium bromide/formoterol inhaled: (400/12 micrograms/dose inhaler) 1 puff twice daily

» Global Initiative for Chronic Obstructive Lung Disease (GOLD) group A patients are characterized by few symptoms (Modified British Medical Research Council [mMRC] 0-1 or COPD Assessment Test [CAT] <10) and low risk of exacerbations (0-1 exacerbations per year, not requiring hospitalization); group B by more symptoms (mMRC ≥2 or CAT ≥10) and low risk of exacerbations (0-1 exacerbations per year, not requiring hospitalization); and group E by a high risk of exacerbations (≥2 exacerbations per year, or ≥1 requiring hospitalization) and any level of symptoms.[1]

» GOLD advises 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 dyspnea/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,

Ongoing

changing inhaler device or molecules may be considered.[1]

» A LABA/LAMA combination may provide a better therapeutic effect without increasing the adverse effects of each class.[105] [109] [110] [111] [112] Systematic reviews and meta-analyses have found that combination therapy with a LABA/LAMA:

» reduces exacerbation rate compared with monotherapy;

» is associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild/moderate COPD, compared with placebo;[113]

» improves FEV_1 and modestly reduces risk of pneumonia in patients with stable chronic obstructive pulmonary disease, but increases odds of all-cause death from 1% to 1.4%.[114]

» Dyspnea 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

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

OR

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

» 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.[97]

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

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» SAMAs should not be prescribed with a long-acting muscarinic antagonist (LAMA). SABAs include albuterol and levalbuterol.

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. See Smoking cessation .

» Depending on local guidelines, patients should be vaccinated against influenza virus, *Streptococcus pneumoniae* , pertussis (whooping cough), varicella-zoster virus (shingles), respiratory syncytial virus, and coronavirus disease 2019 (COVID-19).[1] [231] Vaccination against influenza is associated with fewer exacerbations of COPD.[232] [233]

» 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.[164] [165] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at subsequent appointments can improve inhaler technique.[167]

» 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 medication has been shown to modify the long-term decline in lung function, and the primary goal of pharmacotherapy is to control symptoms and prevent complications. 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 comprises aerobic exercise, strength training, and education, and should be started early in the disease course.[1] [193] [194] GOLD guidelines recommend pulmonary rehabilitation for patient groups B and E.[1]

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» Pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.[195]

» A large US cohort study found that initiation of pulmonary rehabilitation within 90 days of hospital discharge following an acute exacerbation of COPD was significantly associated with lower mortality risk at 1 year and fewer rehospitalizations at 1 year.[198] [199] However, starting pulmonary rehabilitation before hospital discharge could be associated with a higher 12-month mortality, so is not recommended.[200]

adjunct **oxygen therapy and/or ventilatory support**

Treatment recommended for SOME patients in selected patient group

» GOLD guidelines recommend long-term oxygen therapy in stable patients who have: PaO_2 ≤7.3 kPa (55 mmHg) or SaO_2 ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg) or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).[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 hypoxemia. The ATS defines severe hypoxemia as either: PaO_2 ≤7.3 kPa (55 mmHg) or oxygen saturation as measured by pulse oximetry (SpO_2) ≤88%; or PaO_2 7.5 to 7.9 kPa (56-59 mmHg) or SpO_2 of 89% plus one of the following: edema, hematocrit ≥55%, or P pulmonale on an ECG.[208]

» 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.[208]

» Supplemental oxygen should be titrated to achieve SaO_2 ≥90%.[1] 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.

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» Oxygen therapy helps minimize pulmonary hypertension by decreasing pulmonary artery pressure, and improves exercise tolerance and quality of life. It has been shown to improve survival.[1] [66]

» 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 hypoxemia.[208] However, the ATS suggests not prescribing long-term oxygen therapy in adults with COPD who have moderate chronic resting room air hypoxemia (SpO_2 of 89% to 93%).[208]

» For patients who have COPD and obstructive sleep apnea, ventilatory support with continuous positive airway pressure (CPAP) can improve survival and reduce hospital admissions.[1] [73] Noninvasive ventilation is occasionally used in patients with very severe but stable COPD, although the optimal timing for initiation and best selection criteria for candidates is unclear.[1] [212]

» Guidelines from the ATS suggest the use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD.[215] The European Respiratory Society and Canadian Thoracic Society have issued similar guidance.[216] [217]

»

adjunct **ensifentrine**

Treatment recommended for SOME patients in selected patient group

Primary options

» ensifentrine inhaled: 3 mg inhaled via nebulizer twice daily

» Ensifentrine is a selective phosphodiesterase-3 (PDE-3) and PDE-4 inhibitor approved in the US for the maintenance treatment of COPD in adults. It combines bronchodilator and nonsteroidal anti-inflammatory effects within a single molecule. Ensifentrine may be considered as an add-on bronchodilator for patients with stable COPD taking long-acting beta-2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) who have persistent dyspnea symptoms.[1] Clinical benefits were apparent when used as monotherapy and with other maintenance therapies.[141] Nonetheless, enfensitrine's place in therapy requires further study.

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adjunct **mucolytic**

Treatment recommended for SOME patients in selected patient group

Primary options

» acetylcysteine: consult specialist for guidance on dose

» Patients with the chronic bronchitis phenotype of COPD often produce thick sputum on a frequent basis. Mucolytic agents (erdosteine, carbocysteine, and acetylcysteine) 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.[190] [191][192] Treatment with mucolytic agents such as carbocysteine and acetylcysteine may reduce exacerbations and modestly improve health status in patients not receiving inhaled corticosteroid (ICS).[1] However, erdosteine may have a significant effect on mild exacerbations whether or not the patient is taking ICS.[1] Erdosteine and carbocysteine are not available in the US.

adjunct **theophylline**

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 has modest effects on lung function in moderate to severe COPD.[153] A large randomized controlled trial found no effect of oral theophylline alone or with prednisone on exacerbations of severe COPD.[154] Experts may prescribe theophylline after a patient has exhausted all options for inhaled therapies. Toxicity is dose-related. Theophylline is not recommended unless other long-term bronchodilator treatments are unavailable or unaffordable.[1]

adjunct **bronchoscopic intervention or surgery**

Treatment recommended for SOME patients in selected patient group

» Surgical interventions are the last step in the management of COPD, and include bullectomy, lung volume reduction surgery, and

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lung transplant.[218] [219] They are used to improve lung dynamics, exercise adherence, and quality of life.[219] Lung volume reduction surgery is indicated in patients with very severe airflow limitation, and especially in patients with localized upper lobe disease and lower than normal exercise capacity.[218] One meta-analysis found an increased risk of early mortality in patients who underwent lung volume reduction surgery compared to standard care; however, no significant difference was observed in overall mortality.[220] Bullectomy is an option in COPD patients with dyspnea in whom CT reveals huge bullae occupying at least 30% of the hemithorax. Severely poor functional status and severe decrease in FEV_1 (<500 mL) make these options less favorable. Endobronchial valve insertion can produce clinically meaningful improvements in appropriately selected patients with COPD.[220] [221] [222] The procedure may be most beneficial in patients whose dyspnea is primarily due to hyperinflation and air trapping in the air spaces distal to the terminal bronchioles, which manifests as emphysema with markedly increased residual volume. Contraindications include active lung infection and incomplete lobar fissures (<80%).[223] The most common adverse events associated with endobronchial valve insertion are pneumothorax and exacerbation.[220]

» Criteria for referral for lung transplantation include:[224]

» Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) score 5-6 with additional factor(s) present suggestive of increased risk of mortality: frequent acute exacerbations, increase in BODE score >1 over past 24 months, pulmonary artery to aorta diameter >1 on CT scan, and/or FEV_1 20% to 25% predicted.

» Clinical deterioration despite maximal treatment including medication, pulmonary rehabilitation, oxygen therapy, and, as appropriate, nocturnal noninvasive positive pressure ventilation.

» Poor quality of life unacceptable to the patient.

» For a patient who is a candidate for bronchoscopic or surgical lung volume reduction (LVR), simultaneous referral for both lung transplant and LVR evaluation is appropriate.

»

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» Lung transplantation has been shown to improve quality of life and functional capacity.[219] However, lung transplantation does not appear to confer a survival benefit.[225]

adjunct **palliative care**

Treatment recommended for SOME patients in selected patient group

» Palliative therapies to improve symptoms of dyspnea, offer nutritional support, address anxiety and depression, and reduce fatigue may benefit patients with COPD who experience these despite optimal medical therapy. 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.[1] [226] Opioid analgesics, fans, neuromuscular electrical stimulation, and chest wall vibration can relieve dyspnea.[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.[227] Another study found that regular, low-dose, oral sustained-release morphine for 4 weeks improved disease-specific health status in patients with COPD and refractory breathlessness.[228]

» 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.[229]

» Acupuncture and acupressure may also improve breathlessness and quality of life in patients with advanced COPD.[230]

GOLD group A, B, or E: persistent exacerbations after initial therapy

1st **LABA/LAMA or LABA/LAMA/ICS**

Primary options

LABA/LAMA

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

OR

LABA/LAMA

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

OR

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LABA/LAMA

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

OR

LABA/LAMA

» aclidinium bromide/formoterol inhaled: (400/12 micrograms/dose inhaler) 1 puff twice daily

OR

LABA/LAMA/ICS

» fluticasone furoate/umeclidinium/vilanterol inhaled: (100/62.5/25 micrograms/dose inhaler) 1 puff once daily

OR

LABA/LAMA/ICS

» fluticasone furoate/vilanterol inhaled: (100/25 micrograms/dose inhaler) 1 puff once daily
-or-
» fluticasone propionate/salmeterol inhaled: (250/50 micrograms/dose inhaler) 1 puff twice daily
-or-
» budesonide/formoterol inhaled: (160/4.5 micrograms/dose inhaler) 2 puffs twice daily
-or-
» mometasone/formoterol inhaled: (100/5 micrograms/dose inhaler; 200/5 micrograms/dose inhaler) 2 puffs twice daily

--AND--

» tiotropium inhaled: (18 micrograms/capsule inhaler) 18 micrograms (1 capsule) once daily; (2.5 micrograms/dose inhaler) 5 micrograms (2 sprays) once daily
-or-
» umeclidinium inhaled: (62.5 micrograms/dose inhaler) 62.5 micrograms (1 puff) once daily
-or-
» aclidinium bromide inhaled: (400 micrograms/dose inhaler) 400 micrograms (1 puff) twice daily
-or-
» glycopyrrolate inhaled: (25 micrograms/vial nebulizer inhalation solution) 25 micrograms nebulized twice daily using Magnair® nebulizer device

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» Global Initiative for Chronic Obstructive Lung Disease (GOLD) group A patients are characterized by few symptoms (Modified British Medical Research Council [mMRC] 0-1 or COPD Assessment Test [CAT] <10) and low risk of exacerbations (0-1 exacerbations per year, not requiring hospitalization); group B by more symptoms (mMRC ≥2 or CAT ≥10) and low risk of exacerbations (0-1 exacerbations per year, not requiring hospitalization); and group E by a high risk of exacerbations (≥2 exacerbations per year, or ≥1 requiring hospitalization) and any level of symptoms.[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 LABA/LAMA.

» Blood eosinophil counts can identify patients who are more likely to respond to an inhaled corticosteroid (ICS).[76] [77] [78] 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.[134] Former smokers are more corticosteroid-responsive than current smokers at any eosinophil count.[79]

» Escalation to triple therapy with LABA/LAMA/ICS may be considered for patients on long-acting bronchodilator monotherapy if their peripheral eosinophil count is ≥300 cells/microliter. ICS is unlikely to be beneficial in patients whose blood eosinophil count is <100 cells/microliter.[1]

» Patients who take LABA/LAMA who experience persistent exacerbations and whose blood eosinophils are ≥100 cells/microliter 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 hospitalization.[80] [88] [89] [90] [91] [92] [93] [94][95] One randomized 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.[135] Another randomized controlled trial had similar findings in terms of mortality in the triple therapy arm (budesonide/glycopyrrolate/formoterol), but only at the higher dose of ICS.[95] [136] For both studies, there were no differences in mortality compared with LABA/ICS.[95] [135]

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[136] 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 nonsignificant trend for lower mortality with triple therapy compared with non-ICS treatments.[137] These results are strengthened by findings from a meta-analysis of over 200 studies: triple therapy provided a significant reduction in mortality versus dual therapy, although was associated with greater risk of pneumonia. No differences were observed between regimens in lung function or health-related quality of life.[138]

» 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 hospitalization in the past year and who have symptoms of dyspnea or reduced exercise tolerance despite LABA/LAMA dual therapy.[96] UK guidelines recommend the use of LABA/LAMA/ICS in patients who have an exacerbation requiring hospitalization, or two moderate exacerbations within a year, despite dual therapy with LABA/LAMA.[2]

» LABA/ICS is not recommended by GOLD. However, a patient with COPD who previously had exacerbations that responded to LABA/ICS (and has no current exacerbations) may continue on LABA/ICS; high symptom load may merit escalation to LABA/LAMA/ICS in this patient population. If a patient currently receiving LABA/ICS has no relevant exacerbation history, consider switching to LABA/LAMA. Patients on LABA/ICS with current exacerbations and blood eosinophil count <100 cells/microliter may be candidates for changing to LABA/LAMA. Those with current exacerbations and blood eosinophil count ≥100 cells/microliter while using LABA/ICS should be escalated to triple therapy by addition of a LAMA.[1] Patients with blood eosinophils ≥300 cells/microliter are at greatest risk of exacerbations after withdrawing ICS.[81]

plus **short-acting bronchodilator**

Treatment recommended for ALL patients in selected patient group

Primary options

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

OR

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

OR

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

» 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.[97] Ipratropium, a SAMA, may have a small benefit over SABAs in improving health-related quality of life.[97] SAMAs should be discontinued if a long-acting muscarinic antagonist (LAMA) is prescribed. SABAs include albuterol and levalbuterol.

» 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. See Smoking cessation .

» Depending on local guidelines, patients should be vaccinated against influenza virus, *Streptococcus pneumoniae* , pertussis (whooping cough), varicella-zoster virus (shingles), respiratory syncytial virus, and coronavirus disease 2019 (COVID-19).[1] [231] Vaccination against influenza is associated with fewer exacerbations of COPD.[232] [233]

» 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.[164] [165] Demonstration of inhaler use by a clinician, device selection, and reviewing technique at

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subsequent appointments can improve inhaler technique.[167]

» 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 medication has been shown to modify the long-term decline in lung function, and the primary goal of pharmacotherapy is to control symptoms and prevent complications. 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 comprises aerobic exercise, strength training, and education, and should be started early in the disease course.[1] [193] [194] GOLD guidelines recommend pulmonary rehabilitation for patient groups B and E.[1]

» Pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function, and enhances a sense of control to a moderately large and clinically significant extent.[195]

» A large US cohort study found that initiation of pulmonary rehabilitation within 90 days of hospital discharge following an acute exacerbation of COPD was significantly associated with lower mortality risk at 1 year and fewer rehospitalizations at 1 year.[198] [199] However, starting pulmonary rehabilitation before hospital discharge could be associated with a higher 12-month mortality, so is not recommended.[200]

adjunct **oxygen therapy and/or ventilatory support**

Treatment recommended for SOME patients in selected patient group

» GOLD guidelines recommend long-term oxygen therapy in stable patients who have: PaO_2 ≤7.3 kPa (55 mmHg) or SaO_2 ≤88%, with or without hypercapnia confirmed twice over a 3-week period; or PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg) or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).[1]

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» 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 hypoxemia. The ATS defines severe hypoxemia as either: PaO_2 ≤7.3 kPa (55 mmHg) or oxygen saturation as measured by pulse oximetry (SpO_2) ≤88%; or PaO_2 7.5 to 7.9 kPa (56-59 mmHg) or SpO_2 of 89% plus one of the following: edema, hematocrit ≥55%, or P pulmonale on an ECG.[208]

» 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.[208]

» Supplemental oxygen should be titrated to achieve SaO_2 ≥90%.[1] 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 minimize pulmonary hypertension by decreasing pulmonary artery pressure, and improves exercise tolerance and quality of life. It has been shown to improve survival.[1] [66]

» 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 hypoxemia.[208] However, the ATS suggests not prescribing long-term oxygen therapy in adults with COPD who have moderate chronic resting room air hypoxemia (SpO_2 of 89% to 93%).[208]

» For patients who have COPD and obstructive sleep apnea, ventilatory support with continuous positive airway pressure (CPAP) can improve survival and reduce hospital admissions.[1] [73] Noninvasive ventilation is occasionally used in patients with very severe but stable COPD, although the optimal timing for initiation and best selection criteria for candidates is unclear.[1] [212] [213]

» Guidelines from the ATS suggest the use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD.[215] The European Respiratory Society

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and Canadian Thoracic Society have issued similar guidance.[216] [217]

adjunct **roflumilast**

Treatment recommended for SOME patients in selected patient group

Primary options

» roflumilast: 500 micrograms orally once daily

» Roflumilast, an oral phosphodiesterase-4 (PDE-4) inhibitor, may be prescribed for patients taking long-acting beta-2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) who have persistent exacerbations and whose blood eosinophils are <100 cells/microliter, and for patients taking LABA/LAMA/inhaled corticosteroid (ICS) who have persistent exacerbations.[1]

» Roflumilast should be considered in patients with FEV_1 <50% predicted and chronic bronchitis, particularly if they have had at least one hospitalization 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 long-acting beta-2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) who have persistent exacerbations and whose blood eosinophils are <100 cells/microliter, and for patients taking LABA/LAMA/inhaled corticosteroid (ICS) who have persistent exacerbations.[1]

» Azithromycin increases the risk of colonization with macrolide-resistant organisms and should not be prescribed for patients with hearing impairment, resting tachycardia, or apparent risk of QTc prolongation.[148] Azithromycin should be considered preferentially, but not only, in former smokers with persistent exacerbations despite appropriate therapy.[1]

» Before starting prophylactic antibiotics, baseline ECG and liver function tests should be performed, a sputum sample obtained for culture and sensitivity (including tuberculosis testing),

Ongoing

the patient's sputum clearance technique should be optimized, and bronchiectasis should be excluded with a CT scan.[2] [149] 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.[149] If antibiotic therapy is not effective it should be stopped.

adjunct **dupilumab**

Treatment recommended for SOME patients in selected patient group

Primary options

» dupilumab: 300 mg subcutaneously every 2 weeks

» Dupilumab, an interleukin (IL)-4 receptor antagonist monoclonal antibody, may be considered for patients with moderate to severe COPD taking long-acting beta-2 agonist (LABA)/long-acting muscarinic antagonist (LAMA)/inhaled corticosteroid (ICS) with a history of exacerbations, chronic bronchitis, and blood eosinophils ≥300 cells/microliter.[1] [151] [152] Dupilumab should not be used for relief of acute bronchospasm. Dupilumab is approved in the US and Europe for add-on maintenance treatment in adults with uncontrolled COPD characterized by elevated blood eosinophils.

» Adverse effects include injection site reactions.

adjunct **mucolytic**

Treatment recommended for SOME patients in selected patient group

Primary options

» acetylcysteine: consult specialist for guidance on dose

» Patients with the chronic bronchitis phenotype of COPD often produce thick sputum on a frequent basis. Mucolytic agents (erdosteine, carbocysteine, and acetylcysteine) 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.[190] [191] [192] Treatment with mucolytic agents such as carbocysteine and acetylcysteine may reduce exacerbations and modestly improve health status in patients not receiving inhaled corticosteroid (ICS).[1] However, erdosteine may have a significant effect on mild exacerbations whether or not

Ongoing

the patient is taking ICS.[1] Erdosteine and carbocysteine are not available in the US.

adjunct **theophylline**

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 has modest effects on lung function in moderate to severe COPD.[153] A large randomized controlled trial found no effect of oral theophylline alone or with prednisone on exacerbations of severe COPD.[154] Experts may prescribe theophylline after a patient has exhausted all options for inhaled therapies. Toxicity is dose-related. Theophylline is not recommended unless other long-term bronchodilator treatments are unavailable or unaffordable.[1]

adjunct **bronchoscopic intervention or surgery**

Treatment recommended for SOME patients in selected patient group

» Surgical interventions are the last step in the management of COPD, and include bullectomy, lung volume reduction surgery, and lung transplant.[218] [219] They are used to improve lung dynamics, exercise adherence, and quality of life.[219] Lung volume reduction surgery is indicated in patients with very severe airflow limitation, and especially in patients with localized upper lobe disease and lower than normal exercise capacity.[218] One meta-analysis found an increased risk of early mortality in patients who underwent lung volume reduction surgery compared to standard care; however, no significant difference was observed in overall mortality.[220] Bullectomy is an option in COPD patients with dyspnea in whom CT reveals huge bullae occupying at least 30% of the hemithorax. Severely poor functional status and severe decrease in FEV_1 (<500 mL) make these options less favorable. Endobronchial valve insertion can produce clinically meaningful improvements in appropriately selected patients with COPD.[220] [221] [222] The procedure may be most beneficial in patients whose dyspnea is primarily due to hyperinflation and air trapping in the air spaces distal to the terminal

Ongoing

bronchioles, which manifests as emphysema with markedly increased residual volume. Contraindications include active lung infection and incomplete lobar fissures (<80%).[223] The most common adverse events associated with endobronchial valve insertion are pneumothorax and exacerbation.[220]

» Criteria for referral for lung transplantation include:[224]

» Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) score 5-6 with additional factor(s) present suggestive of increased risk of mortality: frequent acute exacerbations, increase in BODE score >1 over past 24 months, pulmonary artery to aorta diameter >1 on CT scan, and/or FEV_1 20% to 25% predicted.

» Clinical deterioration despite maximal treatment including medication, pulmonary rehabilitation, oxygen therapy, and, as appropriate, nocturnal noninvasive positive pressure ventilation.

» Poor quality of life unacceptable to the patient.

» For a patient who is a candidate for bronchoscopic or surgical lung volume reduction (LVR), simultaneous referral for both lung transplant and LVR evaluation is appropriate.

»

» Lung transplantation has been shown to improve quality of life and functional capacity.[219] However, lung transplantation does not appear to confer a survival benefit.[225]

adjunct **palliative care**

Treatment recommended for SOME patients in selected patient group

» Palliative therapies to improve symptoms of dyspnea, offer nutritional support, address anxiety and depression, and reduce fatigue may benefit patients with COPD who experience these despite optimal medical therapy. 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.[1] [226] Opioid analgesics, fans, neuromuscular electrical stimulation, and chest wall vibration can relieve dyspnea.[1]

Ongoing

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.[227] Another study found that regular, low-dose, oral sustained-release morphine for 4 weeks improved disease-specific health status in patients with COPD and refractory breathlessness.[228]

» 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.[229]

» Acupuncture and acupressure may also improve breathlessness and quality of life in patients with advanced COPD.[230]

Emerging

Statins

Statins (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.[235] Although retrospective studies showed decreased rate and severity of exacerbations, hospitalization, and mortality in patients using statin therapy, especially in patients with coexisting cardiovascular disease (CVD) or hyperlipidemia, a prospective study failed to prove this benefit.[236] In a meta-analysis of randomized controlled trials of patients with COPD taking statins, clinical outcomes were better in patients with coexisting CVD, elevated baseline C-reactive protein (CRP), or a high cholesterol level.[237] Further evidence in support of better outcomes in patients with CVD includes a meta-analysis of patients with COPD and comorbid pulmonary hypertension, which revealed improvements in both pulmonary artery pressure and distance walked in 6 minutes following statin therapy.[238] Another meta-analysis compared high-intensity statins with placebo in patients with COPD. 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.[239]

Interventional therapies

Target lobe volume reduction, a novel technique for selective bronchoscopic lung volume resection, has now become available. In this technique, a one-way valve is inserted into the hyperinflated and emphysematous segment, leading to the collapse of the nonfunctional lung segment. Promising reports have been released from case series of patients undergoing this therapy. This approach is an alternative to surgical lung volume reduction in patients with COPD who are likely to require surgery.[240] [241]

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.[242] [243]

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.[244]

Monoclonal antibodies

Monoclonal antibody therapy targeting interleukin (IL)-5 or its receptor may be beneficial in patients with COPD with an eosinophilic phenotype.[245] [246] One Cochrane review found that treatment with mepolizumab or benralizumab resulted in a greater reduction in moderate and severe exacerbations than placebo. A subsequent meta-analysis of patient data from the phase 3 COPD mepolizumab clinical trials indicated that patients with higher blood eosinophil counts experienced greater reduction in moderate and severe exacerbations.[247] Phase 3 studies of mepolizumab and benralizumab in COPD are ongoing. Other monoclonal antibodies in trials for COPD mostly target acute exacerbations.[248]

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 tumor necrosis factor antagonists are among these novel therapies.[249] Long-term (≥6 months) treatment with acetylcysteine may decrease exacerbation prevalence but does not appear to affect exacerbation rate, lung volumes, or FEV_1.[250] Antiplatelet therapy is associated with decreased all-cause mortality in patients with COPD, independent of cardiovascular risk.[251] 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.[252]

Primary prevention

Avoidance of tobacco exposure (both active and passive measures) and toxic fumes are of invaluable importance in primary prevention of COPD.

All smokers should be offered interventions aimed at smoking cessation, including pharmacotherapy and counseling.[1] [55] Although smoking cessation may be associated with minor short-term adverse effects such as weight gain and constipation, its long-term benefits are unquestionable.[55] [56] [57]

Electronic nicotine delivery systems

The use of electronic nicotine delivery systems (ENDS), including e-cigarette and vaping products, as tobacco cessation aids is controversial. Based on available evidence and lack of knowledge about long-term effects on respiratory health, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines concluded that it is not possible to recommend ENDS for smoking cessation.[1] ENDS has been linked to severe pulmonary illness (e-cigarette or vaping product use-associated lung injury [EVALI]).[43] [58] [59] [60] ENDS can contain and emit numerous potentially toxic substances (e.g., nicotine derivatives, polycyclic aromatic hydrocarbons, heavy metals, aldehydes).[43] [59] [60]

The US Preventive Services Task Force (USPSTF) and the 2020 Surgeon General's report note insufficient evidence to evaluate the balance of benefits and risks of e-cigarettes for smoking cessation, and advise that clinicians should direct smokers to Food and Drug Administration (FDA)-approved smoking cessation medicines instead.[55] [61] See Smoking cessation (Management approach) .

Reducing harmful exposures

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.[62]

Shielding measures

Emerging evidence from observational studies conducted during the COVID-19 pandemic suggests that taking shielding measures during winter months (e.g., wearing face masks, reducing social contact, and regular handwashing) may have potential to reduce the risk of exacerbations in people with COPD.[63] [64] [65]

Secondary prevention

People with COPD should receive all recommended vaccinations in accordance with local guidelines.[1] Vaccination against influenza is associated with fewer exacerbations of COPD.[232] [233] Vaccination schedules vary by location; consult local guidance for recommendations.[231] [276]

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. See Smoking cessation .

Vitamin D reduces the rate of moderate/severe exacerbations in patients with levels <25 nanomols/L.[277] [278] Levels should be checked in patients who are hospitalized with an exacerbation of COPD, and supplementation should be given if levels are <25 nanomols/L.[1]

Shielding measures (e.g., mask wearing, minimizing social contact, and frequent hand washing) could be considered during winter months, alongside established COPD management, to help prevent exacerbations of COPD.[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.

Regular medical follow-up is necessary to optimize the treatment. If there is any worsening of symptoms, immediate medical attention is required.

Self-management interventions

Action plans for acute exacerbations of COPD are associated with improvements in health-related quality of life and fewer admissions to the hospital for respiratory problems.[155]

Self-management plans should include personalized advice on:[1]

- Breathlessness and stress management techniques
- Energy conservation
- Avoiding aggravating factors
- How to monitor symptoms
- How to manage worsening symptoms
- Contact information to use in the event of an exacerbation

Studies have found a beneficial effect of cognitive behavioral therapy (CBT) on outcomes including symptoms of depression and anxiety, quality of life, and frequency of emergency department visits.[159] [160] [161]

Patients should be encouraged to:[162] [163]

- Quit active or passive smoking
- Avoid environmental exposure to toxic fumes
- Stay as healthy and active as possible
- Subscribe to health coaching (where available)

See Smoking cessation (Patient discussions) .

Recommend physical activity

Systematic reviews and meta-analyses report that:[173] [179] [180] [181] [182] [275]

- Exercise training on its own can improve physical activity in COPD; greater improvements can be made with the addition of physical activity counseling
- Combined aerobic exercise and strength training is more effective than aerobic exercise alone in increasing leg muscle strength
- Exercise capacity and pulmonary function can be improved with yoga, Qigong, Tai Chi, and other home-based breathing exercises.

One Cochrane review concluded that there is limited evidence for improvement in physical activity with physical activity counseling, exercise training, and pharmacologic management of COPD.[178]

Interventions included in the review assessed in the review had primarily been assessed in single studies. The optimal timing, components, duration, and models for improving physical activity remain unclear.

Consider inhaler device technique

Ask patients to bring their inhalers to clinic to facilitate a review of inhaler use.[1] [167] [168] [169] [170]

- Demonstrate inhaler use and review technique at subsequent appointments; using a placebo device may be most effective for teaching inhaler technique to adults ages ≥65 years,
- Pharmacist-led interventions and lay health coaching can improve inhaler technique and adherence.
- Preferred inhaler device attributes (e.g., small size, rapid onset of symptom relief) have been reported in patient preference studies.[171] [172]

The majority of patients make at least one error in using their inhaler, and incorrect inhaler use is associated with worse disease control.[164] [165] Poor technique is more likely when patients are using multiple devices or have never received inhaler technique training.[166]

Dietary advice and oral supplements

Have been found to improve body weight, quality of life, respiratory muscle strength and 6-minute walk distance.[183] [184]

Nutritional support has not been consistently found to improve lung function.[184]

Preparing for air travel

Optimize the patient's condition prior to air travel and assess their need for inflight oxygen. Advise patients to:[210]

- Inquire about venous thromboembolism prophylaxis, especially before long flights
- Carry all medications and spacer devices in their hand luggage
- Have any emergency medications immediately accessible during the flight
- Consider increased oxygen flow during air travel (if receiving continuous oxygen therapy)

FOLLOW UP

Monitoring

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.

Patients with severe, frequent exacerbations and recently hospitalized patients need follow-up at 2-week to 1-month intervals.

In follow-up sessions, patients should be evaluated to determine:

- Adherence to medical regimen
- Response to therapy
- Inhaler technique
- Adverse effects of therapy
- Disease progression

The level of dyspnea at rest and with exercise should be determined, as well as number of exacerbations. Questionnaires such as the COPD Assessment Test (CAT) can be used to assess symptoms.

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

The GOLD guidelines recommend measuring FEV_1 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 characterized 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.

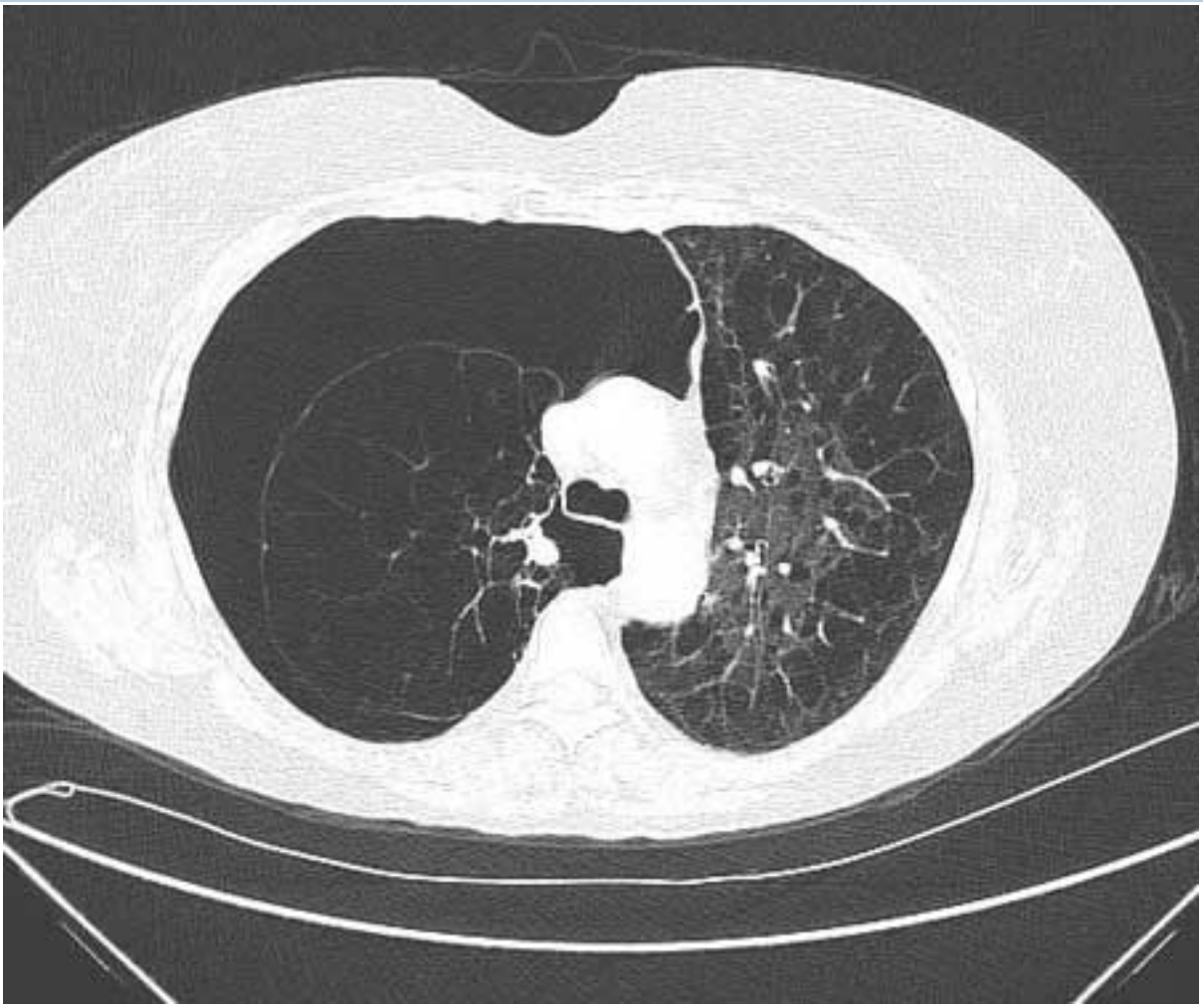
One Cochrane review found that remote monitoring through telehealth technology reduced the risk of hospital readmission in patients with moderate to severe COPD, and may be considered as an adjunct to usual care.[274]

Complications

Complications	Timeframe	Likelihood
cor pulmonale	**long term**	**high**
Cor pulmonale is right-sided heart failure secondary to longstanding COPD. It is caused by chronic hypoxia and subsequent vasoconstriction in pulmonary vasculature that causes pulmonary hypertension and right-sided heart failure. Engorged neck veins, a loud P2, lower-extremity edema, 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.[269]		
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.[273]		
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 colonization are likely causes of increased vulnerability to infections. Use of inhaled corticosteroids is also associated with increased risk of pneumonia in patients with COPD.[124] [266] [267] Use of antibiotic therapy has shown some benefit.[268] Usual treatment time is around 7-14 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. It is estimated that patients with COPD are 1.9 times more likely to die from suicide than those without COPD.[157] If any mood change occurs, a psychiatric evaluation may be necessary.		
pneumothorax	**variable**	**medium**
Occurs because of lung parenchyma damage with subpleural bulla formation and rupture. Spontaneous pneumothorax is very common with chronic severe cough or chest trauma, and may be life-threatening. High levels of suspicion are necessary for prompt diagnosis. Chest x-ray or chest computed tomography (CT) confirms the diagnosis.		

FOLLOW UP

Complications	Timeframe	Likelihood



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

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

respiratory failure	**variable**	**medium**
A study of a large number of patients with COPD and acute respiratory failure reported in-hospital mortality of 17% to 49%.[265] Therapy includes noninvasive positive pressure ventilation and/or mechanical ventilation.		

anemia	**variable**	**medium**
Anemia is more prevalent than previously thought, affecting almost 25% of patients with COPD.[270] A low hematocrit indicates a poor prognosis in patients receiving long-term oxygen treatment.[271] One meta-analysis found that patients with comorbid anemia were also more likely to spend longer periods of time in the hospital than those without comorbid anemia, as well as experiencing higher rates of mortality.[272]		

Complications	Timeframe	Likelihood
polycythemia	**variable**	**medium**
Secondary polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers. It can be identified by hematocrit >55%. Many times these patients require supplemental home oxygen.		

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 FEV_1, which is a part of pulmonary function testing. A meta-regression analysis showed a significant correlation between increased FEV_1 and lower risk of COPD exacerbation.[257]

In addition to the FEV_1, other factors that predict prognosis are weight (very low weight is a negative prognostic factor, with one meta-analysis identifying a significant association between low body mass index and accelerated FEV_1 decline), distance walked in 6 minutes, and degree of shortness of breath with activities.[258] [259] These factors, known as the Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index, can be used to provide information on prognosis for 1-year, 2-year, and 4-year survival.[260] One study revealed that plasma pro-adrenomedullin concentration plus BODE index is a better prognostic tool than BODE index alone.[261] Elevation of adrenomedullin, arginine vasopressin, atrial natriuretic peptide, and C-reactive protein is associated with increased risk of death in patients with stable COPD.[262] [263] 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, dyspnea, and previous severe exacerbations) is proved to be superior to BODE index in predicting prognosis for patients with COPD.[264] 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.[265]

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

Diagnostic guidelines

International

Global strategy for the diagnosis, management, and prevention of COPD (https://goldcopd.org/2025-gold-report) [1]

Published by: Global Initiative for Chronic Obstructive Lung Disease **Last published:** 2025

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (https://www.nice.org.uk/guidance/ng115) [2]

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

Treatment guidelines

International

Pulmonary rehabilitation for adults with chronic respiratory disease: an official American Thoracic Society clinical practice guideline (https://www.atsjournals.org/page/ajrccm/collections/ats-documents) [193]

Published by: American Thoracic Society **Last published:** 2023

Clinical practice guideline on pharmacotherapy in patients with stable COPD (https://cts-sct.ca/guideline-library) [253]

Published by: Canadian Thoracic Society **Last published:** 2023

Management of chronic obstructive pulmonary disease (COPD) (https://www.healthquality.va.gov/guidelines/cd/copd/) [254]

Published by: US Department of Veterans Affairs/Department of Defense **Last published:** 2021

Chronic obstructive pulmonary disease: a 2019 evidence analysis center evidence-based practice guideline (https://www.andeal.org/topic.cfm?menu=5301) [255]

Published by: Academy of Nutrition and Dietetics **Last published:** 2021

Long-term non-invasive ventilation in patients with chronic obstructive pulmonary disease (COPD): 2021 Canadian Thoracic Society clinical practice guideline update (https://cts-sct.ca/guideline-library) [217]

Published by: Canadian Thoracic Society **Last published:** 2021

Pharmacologic management of chronic obstructive pulmonary disease (https://www.thoracic.org/statements/copd.php) [96]

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

Home oxygen therapy for adults with chronic lung disease (https://www.thoracic.org/statements/copd.php) [208]

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

Long-term noninvasive ventilation in chronic stable hypercapnic chronic obstructive pulmonary disease (https://www.thoracic.org/statements/guideline-implementation-tools/index.php) [215]

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

Global strategy for the diagnosis, management, and prevention of COPD (https://goldcopd.org/2025-gold-report) [1]

Published by: Global Initiative for Chronic Obstructive Lung Disease **Last published:** 2025

International

An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease (https://www.thoracic.org/statements/copd.php) [6]

Published by: American Thoracic Society; European Respiratory Society **Last published:** 2014

Withdrawal of inhaled corticosteroids in COPD (https://channel.ersnet.org/channel-25-guidelines) [132]

Published by: European Respiratory Society **Last published:** 2020

Guidelines on long-term home non-invasive ventilation for management of COPD (https://channel.ersnet.org/channel-25-guidelines) [216]

Published by: European Respiratory Society **Last published:** 2019

The COPD-X plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease (https://copdx.org.au) [256]

Published by: Lung Foundation Australia; Thoracic Society of Australia and New Zealand **Last published:** 2023

British Thoracic Society clinical statement on pulmonary rehabilitation (https://thorax.bmj.com/content/78/Suppl_5/s2) [194]

Published by: British Thoracic Society **Last published:** 2023

Guideline for the use of long-term macrolides in adults with respiratory disease (https://www.brit-thoracic.org.uk/quality-improvement/guidelines) [149]

Published by: British Thoracic Society (UK) **Last published:** 2020

Chronic obstructive pulmonary disease in over 16s: diagnosis and management (https://www.nice.org.uk/guidance/ng115) [2]

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

Online resources

1. 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) *(external link)*

EVIDENCE TABLES

Evidence tables

What are the effects of integrated disease management (IDM) interventions for people with chronic obstructive pulmonary disease (COPD)?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

Cochrane Library

View the full source Cochrane Clinical Answer (https://www.cochranelibrary.com/cca/doi/10.1002/cca.3877/full)

Evidence A *

Confidence in the evidence is high or moderate to high where GRADE has been performed and the intervention is more effective/beneficial than the comparison for key outcomes.

Population: Adults with COPD
Intervention: IDM [a]
Comparison: Usual care (regular follow-up visits with healthcare providers)

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Quality of life (>6 to 15 months): St. George's Respiratory Questionnaire (SGRQ) [b]	Favors intervention	Moderate
Functional exercise capacity (>6 to 15 months)	Favors intervention	Moderate
Respiratory-related hospital admissions (12 months)	Favors intervention	High
All hospital admissions	Favors intervention	Moderate
Hospital days per patient (all causes)	Favors intervention	Moderate
Emergency Department visits	Favors intervention	Moderate
Number of patients experiencing ≥ 1 exacerbation	No statistically significant difference	GRADE assessment not performed for this outcome
Mortality	No statistically significant difference	GRADE assessment not performed for this outcome
Need for at least one course of oral steroids	No statistically significant difference	GRADE assessment not performed for this outcome

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Need for at least one course of antibiotics	No statistically significant difference	GRADE assessment not performed for this outcome

Note

The Cochrane review which underpins this Cochrane Clinical Answer (CCA) notes that the effects of IDM are better in the short and medium term, and that the effect size was different between included studies and interventions. IDM should be carefully designed and evaluated, consisting of different components which are linked to the personal goals of the patient.

[a] Including organizational, professional, patient-directed, and financial interventions in primary, secondary, and tertiary healthcare settings. See CCA and the underlying Cochrane review for more information on specific interventions and the dominant components of the IDM programs.

[b] Although statistically significant, this result did not quite reach the minimum clinically important difference. The CCA also reports a subgroup analysis for quality of life measured by the Chronic Respiratory Questionnaire. However, this was only reported in two studies and the analysis was underpowered.

How does umeclidinium compare with placebo for people with chronic obstructive pulmonary disease (COPD)?

This table is a summary of the analysis reported in a Cochrane Clinical Answer that focuses on the above important clinical question.

View the full source Cochrane Clinical Answer (https://www.cochranelibrary.com/cca/doi/10.1002/cca.1829/full)

Evidence A * Confidence in the evidence is high or moderate to high where GRADE has been performed and the intervention is more effective/beneficial than the comparison for key outcomes.

Population: Adults with moderate-to-severe COPD
Intervention: Umeclidinium (once daily via a dry powder inhaler for 12-52 weeks)
Comparison: Placebo

Outcome	Effectiveness (BMJ rating)†	Confidence in evidence (GRADE)‡
Number of participants with exacerbations requiring corticosteroids, antibiotics, or both at 52 weeks	Favors intervention	High
Quality of life at 24-52 weeks (measured by the St George's Respiratory Questionnaire [SGRQ])	Favors intervention	Moderate
Number of participants with hospital admissions due to COPD exacerbation at 52 weeks (measured by the Transitional Dyspnea Index [TDI])	No statistically significant difference	Low
Improvement in symptoms at 24 weeks	Favors intervention	High
Lung function at 4-52 weeks	Favors intervention	High
Nonfatal serious adverse events	No statistically significant difference	Moderate
Adverse events	No statistically significant difference	Moderate

* Evidence levels

The Evidence level is an internal rating applied by BMJ Best Practice. See the EBM Toolkit (https://bestpractice.bmj.com/info/evidence-tables/) for details.

Confidence in evidence

A - High or moderate to high

B - Moderate or low to moderate

C - Very low or low

† Effectiveness (BMJ rating)

Based on statistical significance, which demonstrates that the results are unlikely to be due to chance, but which does not necessarily translate to a clinical significance.

‡ Grade certainty ratings

High	The authors are very confident that the true effect is similar to the estimated effect.
Moderate	The authors are moderately confident that the true effect is likely to be close to the estimated effect.
Low	The authors have limited confidence in the effect estimate and the true effect may be substantially different.
Very Low	The authors have very little confidence in the effect estimate and the true effect is likely to be substantially different.

BMJ Best Practice EBM Toolkit: What is GRADE? (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/)

Key articles

- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2025 report. 2025 [internet publication]. Full text (https://goldcopd.org/2025-gold-report)
- National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Jul 2019 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng115)
- Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020 May 1;201(9):e56-69. Full text (https://www.atsjournals.org/doi/10.1164/rccm.202003-0625ST) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32283960?tool=bestpractice.bmj.com)
- Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020 Nov 15;202(10):e121-41. [Erratum in: Am J Respir Crit Care Med. 2021 Apr 15;203(8):1045-6.] Full text (https://www.atsjournals.org/doi/10.1164/rccm.202009-3608ST) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33185464?tool=bestpractice.bmj.com)

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Images

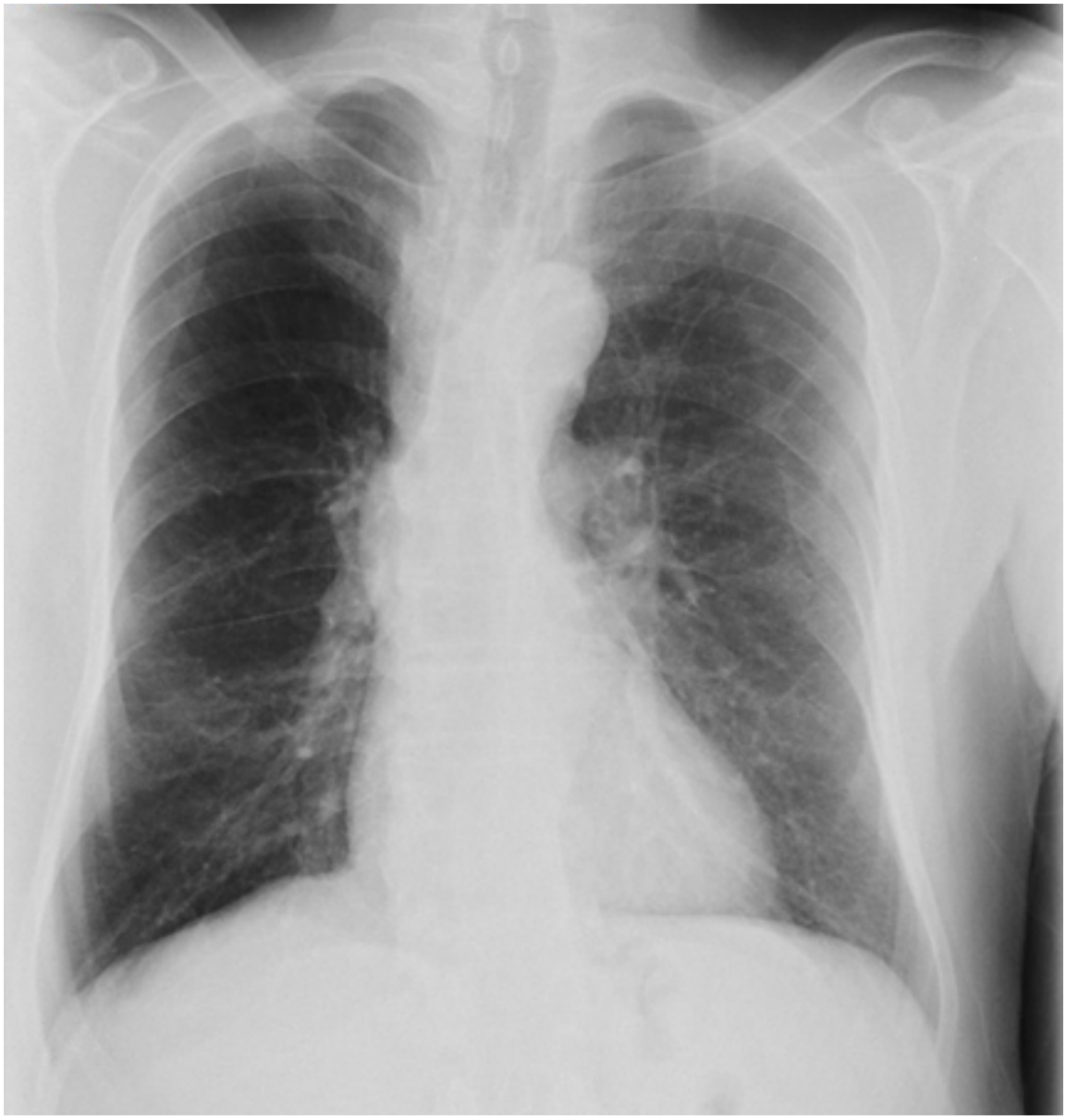

Figure 1: COPD chest x-ray (AP view): hyperinflated lung, flattened diaphragm, increased intercostal spaces

From the collection of Manoochehr Abadian Sharifabad, MD

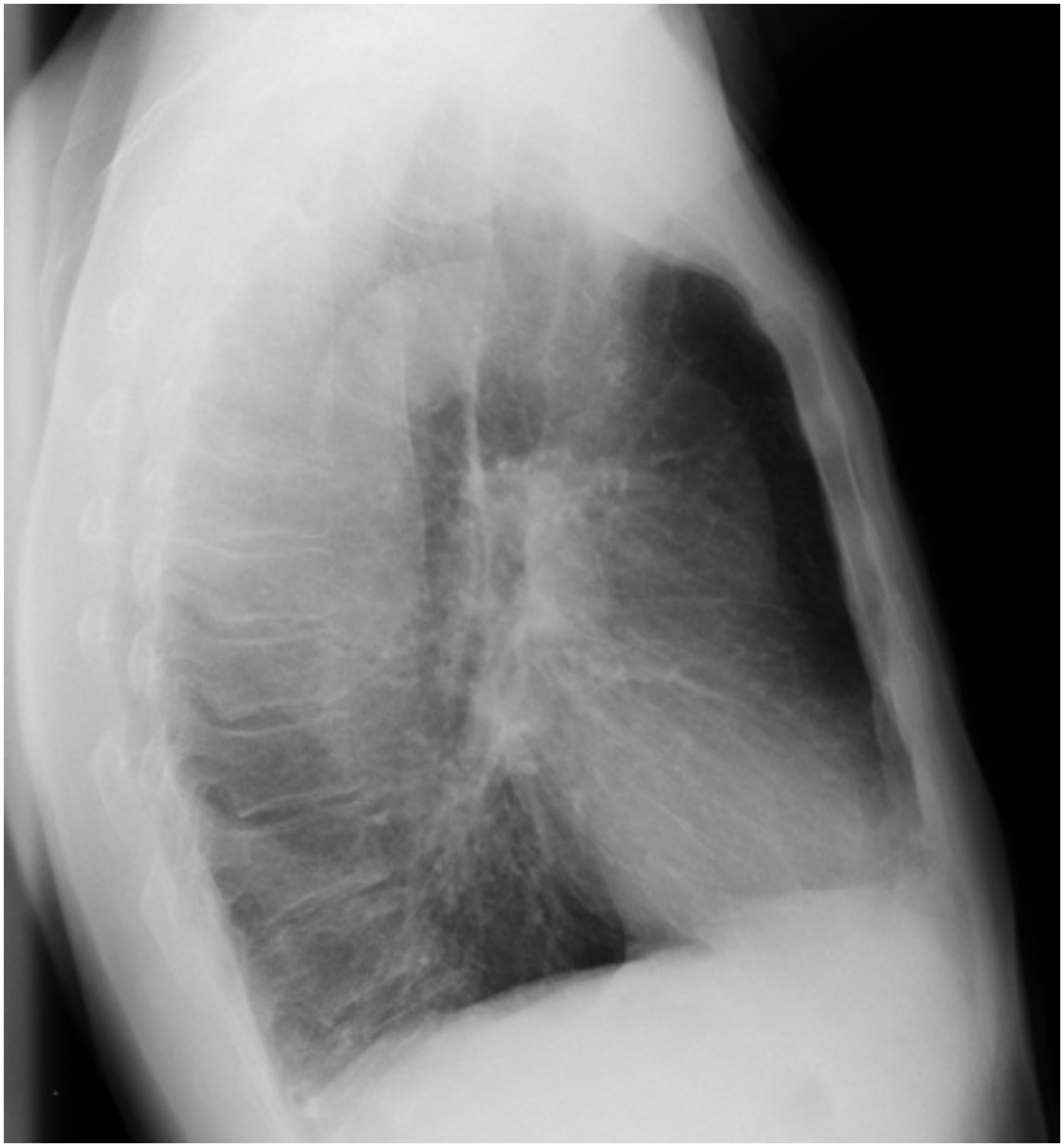

Figure 2: COPD chest x-ray (lateral view): hyperinflated lung, flattened diaphragm, increased antero-posterior diameter (barrel chest) in lateral view

From the collection of Manoochehr Abadian Sharifabad, MD

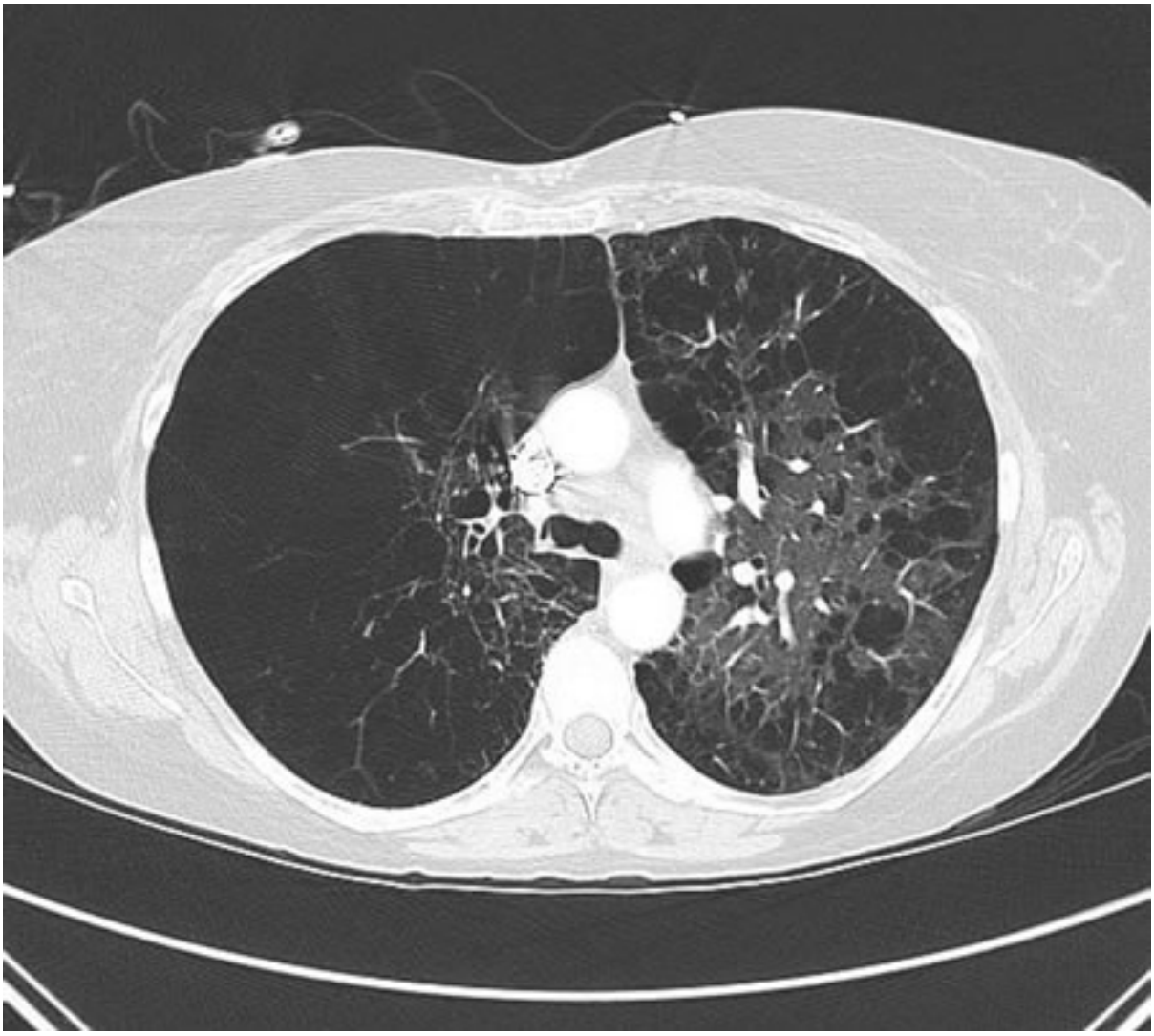

Figure 3: COPD chest CT: hyperinflated lung, emphysematous changes, and increased antero-posterior diameter (barrel chest)

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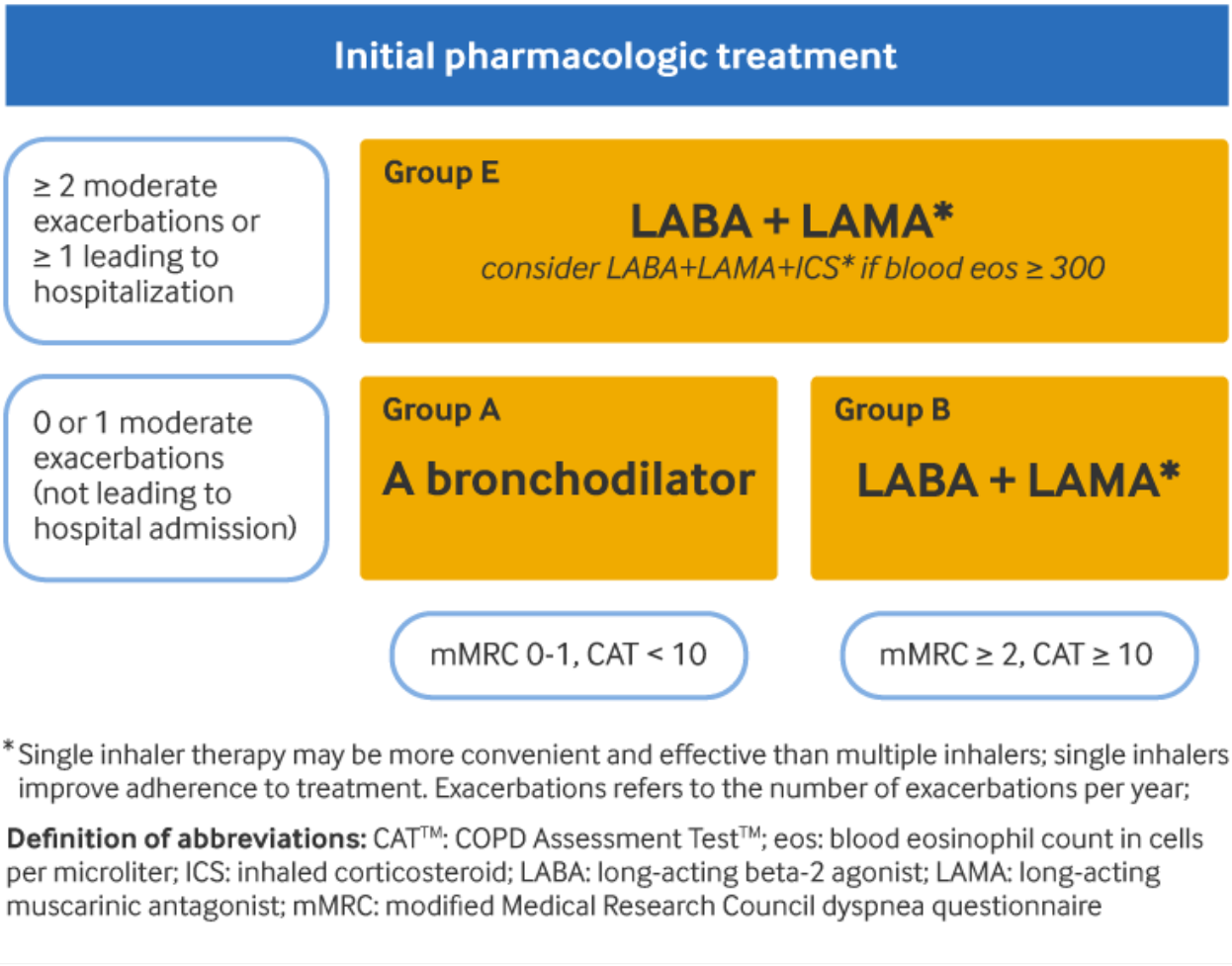

Figure 4: Initial pharmacologic management of COPD

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2025 report); reproduced with permission

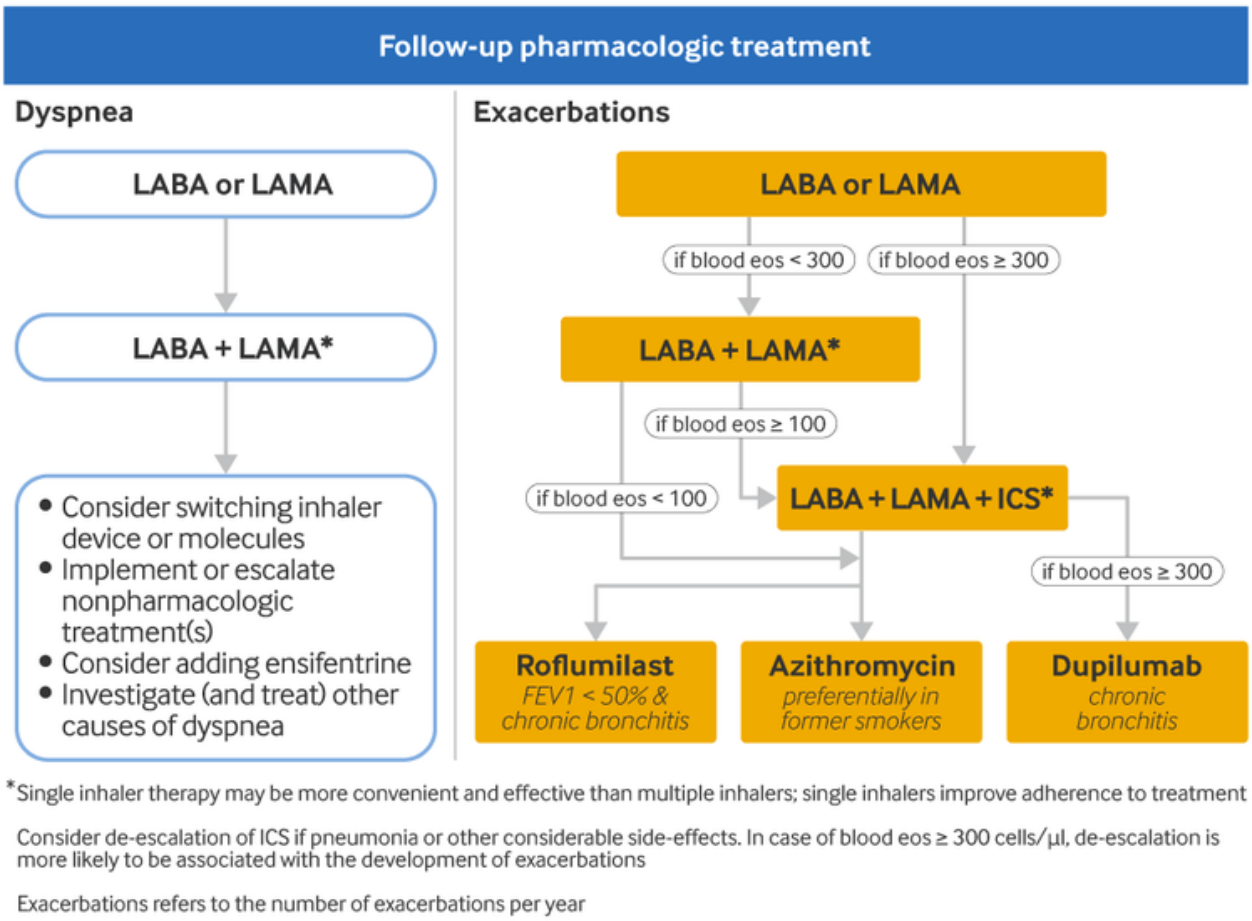

Figure 5: Escalation therapy for patients with COPD. Definition of abbreviations: ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

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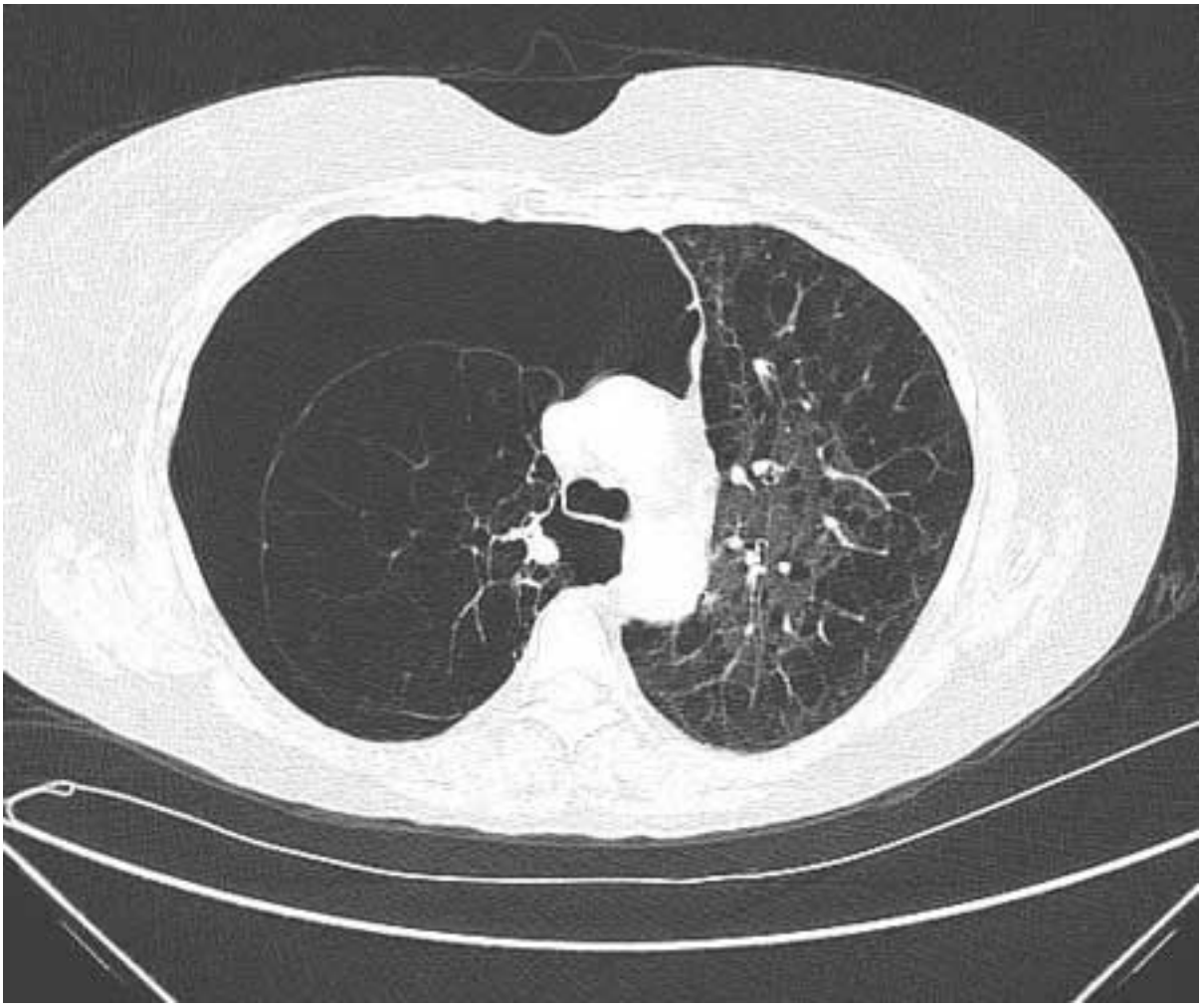

Figure 6: Chest CT: severe COPD changes with right pneumothorax

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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

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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