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Medicine

**SIXTH EDITION
VOLUME 3**

EDITED BY
**John D. Firth
Christopher P. Conlon
Timothy M. Cox**

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Chronic obstructive pulmonary disease

Nicholas S. Hopkinson

ESSENTIALS

Definition

Chronic obstructive pulmonary disease (COPD) is a lung condition caused by the inhalation of noxious materials, principally tobacco smoke, and characterized by airflow limitation that is not fully reversible. Key features are cough, sputum production, and breathlessness. There are chronic progressive symptoms and acute exacerbations. The term COPD incorporates several pathological processes, present to a variable extent in any given individual, involving both the airways (chronic bronchitis) and the lung parenchyma (emphysema). Most COPD patients will have one or more other long-term conditions. COPD is the third leading cause of death worldwide.

COPD should be considered in those over the age of 35 who have (1) exposure to risk factors, usually, but not exclusively, tobacco smoke; (2) a history of chronic progressive respiratory symptoms; (3) airflow limitation that is not fully reversible.

Aetiology

Cigarette smoking is the single most important identifiable risk factor. Worldwide, biomass smoke exposure from domestic heating, cooking, and lighting is also a major contributor. Other risk factors include early life disadvantage, childhood asthma, and occupations with exposure to dust, fumes, and chemicals. There is significant familial risk, but apart from α_1 -antitrypsin deficiency other genetic causes of COPD remain to be established.

Pathology and pathophysiology

Inflammation, protease/antiprotease imbalance and oxidative stress all have a role in producing chronic bronchitis, obstructive bronchiolitis, or small airways disease, and emphysema, which can be centrilobular (centriacinar) or panlobular (panacinar).

The characteristic physiological impairment is a decrease in maximum expiratory airflow that limits the level of ventilation that can be achieved. This is caused by destruction of and damage to airways, combined with a loss of lung elastic recoil due to parenchymal damage. To avoid early airway closure and gas trapping, operating lung volumes rise, increasing the load on the respiratory muscles which are simultaneously at a mechanical disadvantage.

Unequal ventilation of lung units leads to ventilation-perfusion (V/Q) mismatch which can cause hypoxia. Destruction of the pulmonary capillary bed can lead to pulmonary hypertension. Lung hyperinflation can also impair cardiac function. Skeletal muscle impairment associated with physical inactivity and loss of fitness also contributes to symptoms of breathlessness, as may coexisting cardiac disease.

Clinical features

History—Breathlessness is chronic, though there may be some day-to-day variation. Cough and sputum vary between individuals and over time. Smoking status, tobacco, and nontobacco, is essential as well as details of any childhood chest disease and previous and present occupations, particularly exposure to dust, fumes, and chemicals. Exacerbation frequency can be assessed by patient recall. Comorbidities should be actively sought. Use a health status measure such as the COPD assessment test (CAT) routinely.

Examination—Signs of airflow limitation may not be present until there is significant impairment of lung function, but the breathing pattern in COPD is often characteristic, with a prolonged expiratory phase, and there may be signs of overinflation of the chest. Breath sounds are typically quiet. Pulmonary crackles suggest infection or coexistent bronchiectasis. Seek evidence of pulmonary hypertension (oedema, raised venous pressure, tachycardia). Pulse oximetry should be performed routinely.

Investigation

Spirometry—A post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV/FVC) ratio less than 0.70 confirms the presence of airflow limitation that is not fully reversible and is a diagnostic criterion for COPD. The severity of airflow limitation can be graded according to the Global Initiative for Obstructive Lung Disease (GOLD) as mild ($\geq 80\%$ predicted), moderate ($50\text{--}79\%$ predicted), severe ($30\text{--}49\%$ predicted), or very severe ($<30\%$ predicted). Further categorization is based on breathlessness and exacerbation frequency.

Lung function tests—Static lung volumes can be measured to assess the degree of overinflation and gas trapping. Gas transfer measures give evidence of the extent of emphysema.

Arterial blood gases—Confirm the degree of hypoxaemia and hypercapnia in stable patients with oxygen saturations below 93%, or those with clinical signs of respiratory or right heart failure or features of sleep-disordered breathing.

Exercise testing—The incremental shuttle walk test or 6-min walk provide objective evidence of exercise capacity, give prognostic information, and may also be used to evaluate the need for ambulatory oxygen.

Imaging—(1) Chest X-ray may appear normal or show signs of overinflation, pulmonary vascular abnormalities, or other coexisting pathologies. (2) CT scanning can be used to quantify and identify the pattern of emphysema present as well as detecting coexisting bronchiectasis or pulmonary fibrosis.

Other tests—α1 antitrypsin levels and phenotype can be measured, especially in patients who have become symptomatic at an early age or with a strong family history.

Prevention

Stopping smoking is the most effective measure. Action on indoor and outdoor air quality and to address child poverty and early life disadvantage are also important. Physical activity is probably protective.

Management

Stable COPD—treatment is based on an assessment of symptoms, severity of airflow limitation, and the risk of exacerbations.

As well as being a preventive measure, the highest value treatment for COPD is smoking cessation. All patients should receive influenza and pneumococcal vaccination.

Pulmonary rehabilitation, a supervised programme of exercise and education, reduces breathlessness, improves exercise tolerance and health related quality of life, and reduces exacerbation frequency and should be offered to all patients who are limited by breathlessness. It is also highly effective, reducing hospital readmission, when applied post exacerbation.

Pharmacologic therapy—inhaled bronchodilators (β_2 -agonists and/or antimuscarinic agents) are central to symptom management. Short-acting bronchodilators are prescribed on an as needed basis, but long-acting bronchodilators usually in combination are given if symptoms are persistent. Inhaled corticosteroids are indicated in patients having two or more exacerbations/year or in people with more severe airflow obstruction, when they act synergistically with long-acting bronchodilators. Inhaled therapies do not alter the natural history of the disease. Oral theophyllines are less effective and less well tolerated than long-acting bronchodilators, but can provide additional symptom relief when added to long-acting bronchodilators. Long-term azithromycin is effective in some patients with frequent exacerbations.

Palliative measures—These include hand-held battery-powered fans and low dose oral morphine for breathlessness. Discussions about end of life and establishing a ceiling of care are important in people with severe COPD.

Long-term oxygen therapy (≥ 15 h per day) given to patients with chronic respiratory failure ($\text{PaO}_2 \leq 7.3$ kPa or $\text{PaO}_2 < 8.0$ kPa if pulmonary hypertension is present) improves survival.

Other interventions—Lung volume reduction surgery improves survival in carefully selected patients (upper lobe emphysema, poor exercise capacity but condition not too severe for safety).

The evidence for benefit from endobronchial valve placement is also growing. Lung transplantation can be considered in patients with very advanced COPD but is often inappropriate because of comorbidity.

Acute exacerbations of COPD (AECOPD) can be caused by various factors, the commonest being viral or bacterial respiratory tract infections. Most can be managed in the community (many patients are able to self-manage) with short courses of antibiotics and oral corticosteroids. Severe AECOPD are a common reason for admission to hospital, especially in frail individuals or if there is respiratory failure. Treatment includes: (1) controlled oxygen therapy to achieve PaO_2 greater than 8 kPa (60 mm Hg) or SaO_2 88–92%, without inducing significant CO_2 retention; (2) nebulized bronchodilators; (3) antibiotics—if there is increased sputum purulence with increase in dyspnoea and/or increase in sputum volume; (4) corticosteroids—prednisolone 30–40 mg daily for 7 days; and (5) ventilatory support—usually noninvasive, if pH is less than 7.35.

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. It is defined in the joint American Thoracic Society and European Respiratory Society Guidelines as ‘a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences’.

The key clinical features of COPD are breathlessness, cough and sputum production, limitation of daily physical activities and the occurrence of acute exacerbations. The presence of airflow obstruction is required as part of the clinical definition of COPD. The severity of COPD has conventionally been classified according to the severity of airflow obstruction, defined as a reduction in the forced expiratory volume in one second (FEV_1), but this captures only one aspect of the condition.

The term COPD, first introduced in 1965, encompasses several pathological processes which may affect the large and small airways, the lung parenchyma, and the pulmonary vasculature to a varying extent in any individual. This gives rise to a wide range of possible disease phenotypes (Fig. 18.8.1). In the large airways, chronic bronchitis is defined as the presence of a chronic productive cough on most days for 3 months in at least two consecutive years. Chronic bronchitis is characterized by mucus hypersecretion and may occur by itself in the absence of airflow obstruction, particularly in smokers. Conversely, airflow obstruction can occur in the absence of chronic bronchitis. Small airways are destroyed through a process of obliterative bronchiolitis. This, together with emphysema, the destruction of lung parenchyma and consequent loss of lung elastic recoil, produces airflow obstruction. COPD can be associated with flare ups or acute exacerbations which are distressing and can be life-threatening, and are a major burden to patients and health services.

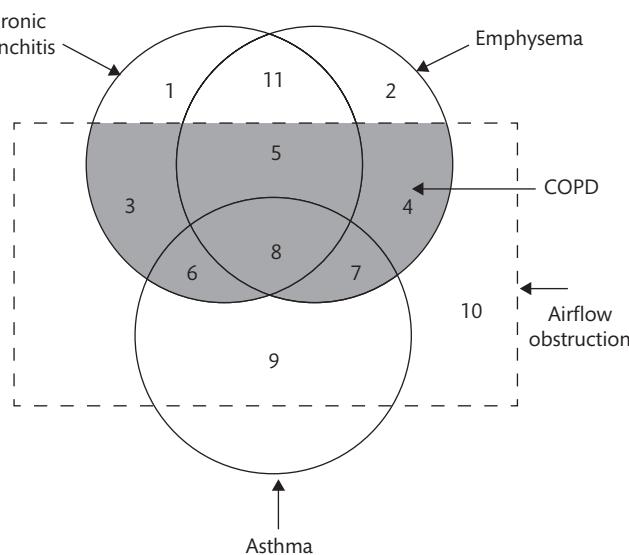


Fig. 18.8.1 Nonproportional Venn diagram of chronic obstructive pulmonary disease (COPD) produced by the American Thoracic Society. The subsets comprising COPD are shaded. Subset areas are not proportional to the actual relative subset sizes. Asthma is by definition associated with reversible airflow obstruction although, in variant asthma, special manoeuvres may be necessary to make the obstruction evident. Patients with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. Because in many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity, patients with unremitting asthma are classified as having COPD (subsets 6, 7, and 8). Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5), and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma who have been exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, which is a feature of chronic bronchitis (subset 6). Persons with chronic bronchitis and/or emphysema without airflow obstruction (subsets 1, 2, and 11) are not classified as having COPD. Patients with airway obstruction due to diseases with known aetiology or specific pathology such as cystic fibrosis or obliterative bronchiolitis (subset 10) are not included in this definition.

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The characteristic lung function abnormality is airflow obstruction measured, by spirometry, as the ratio of the FEV₁ to the vital capacity (VC). A ratio below 70% is usually taken to be required for the diagnosis to be made.

The most effective treatment for COPD is smoking cessation. Pulmonary rehabilitation, a combination of supervised exercise and education, also has a strong evidence base for benefit. Pharmacotherapy can reduce symptoms and exacerbation frequency, but existing therapies have so far demonstrated little effect on the natural history of COPD. For selected individuals with severe emphysema, lung volume reduction surgery can improve prognosis. Long-term oxygen therapy improves survival in hypoxic individuals.

For most patients, COPD is only one of several long-term conditions. Around 80% of individuals with COPD have an additional diagnosis. Patient management needs to reflect this multimorbidity

as well as following a rational approach to the specific COPD phenotype of each individual.

The lungs are at the cutting edge of the social determinants of health. Social class gradients in smoking, together with occupations that expose individuals to dust, fumes, and chemicals, as well as exposure to biomass smoke and an adverse early life environment which impacts on lung development, all mean that the prevalence of COPD increases with increasing poverty.

Aetiology

COPD is caused by the individual's response to the inhalation of noxious materials. This depends on a combination of host factors and exposure. The major risk factor is smoking, but COPD is also associated with occupations where individuals are exposed to dust, fumes, or chemicals (Table 18.8.1). Genetic predisposition, airway hyperreactivity or asthma, and a failure of lung growth are key susceptibility factors.

Fletcher and Peto first demonstrated, in an 8-year study of working men, that smoking was associated with impaired lung function. Prospective life course data, such as from the Framingham study, now show clearly that tobacco smoking is associated with an increased rate of lung function decline (Fig. 18.8.2). There are individual variations in susceptibility to tobacco smoke which are poorly understood but which appear to be heritable to an extent.

COPD is a progressive condition so its prevalence increases with age. Lung function at any given point in time will depend on the rate of decline but also on the peak lung function achieved from which this decline is occurring. Lung function usually peaks around the age of 20 and early life factors are therefore critical. Maternal or paternal asthma, childhood asthma, maternal smoking and childhood respiratory infections are significantly associated with lower FEV₁ in adult life and have been defined as

Table 18.8.1 Risk factors for COPD

Exposures	
Tobacco smoking	Major cause of COPD worldwide
Biomass smoke exposure	Smoke from domestic cooking and heating
Occupational exposures	Mining, industrial occupations, cleaning
Poor nutrition	Lead to impaired lung growth
Passive and <i>in utero</i> smoke exposure	
Susceptibility factors	
Airways hyperreactivity and asthma	
Recurrent bronchopulmonary infections	
Genetic factors	Gene polymorphisms influence lung function decline, specific COPD phenotypes, and avidity of nicotine receptors α-1 antitrypsin deficiency
Female sex	May increase susceptibility to the effects of smoke

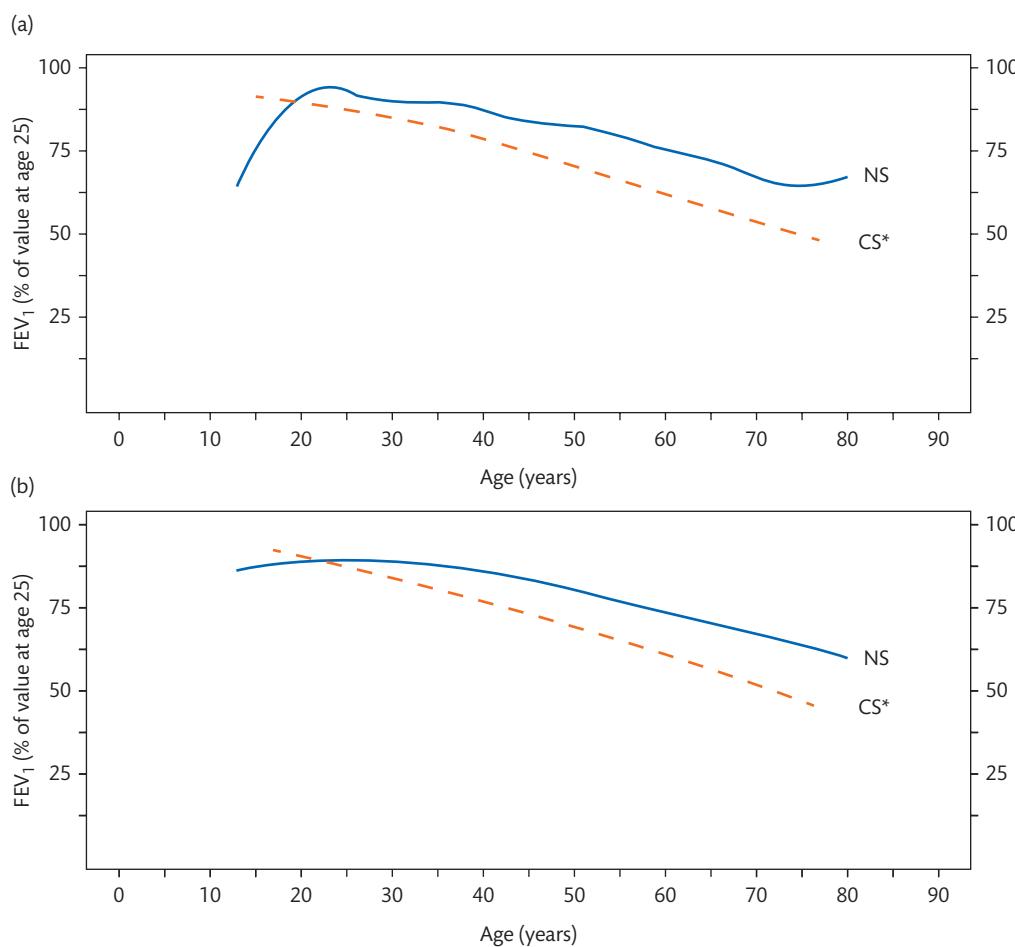


Fig. 18.8.2 Mean FEV₁ values (expressed as percent of its value at the age of 25) by age, for healthy never-smokers (NS), and continuous smokers (CS). (a) Data for males and (b) for females. The mean FEV₁ decline value (and 95% confidence intervals) for males was 38.2 ml (33.9–42.6) and for females 23.9 ml (20.9–27.0), with a *p* value less than 0.001 (**p* < 0.05 versus healthy never-smokers).

Reproduced from Kohansal R, et al. (2009). The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med*, 180(1), 3–10.

'childhood disadvantage factors'. People with these factors have permanently reduced lung function, a more rapid decline in lung function, and a substantially increased COPD risk. Importantly, the impact of childhood disadvantage is as large as that of heavy smoking. *In utero* exposure through maternal smoking is associated with low birth weight and subsequent impaired lung function. It also increases asthma severity symptoms and an increased risk of wheezy illness.

Smoking is itself an addiction mostly starting in childhood. For example, in the United Kingdom 200 000 11–15 year olds start smoking every year. In Pakistan 40% of smokers report that they started before they were 10 years old. The effects of smoking are thus first experienced by people while their lungs are still growing.

Although smoking has been accepted as the major cause of COPD, biomass smoke exposure from wood, charcoal, dried twigs and grass, crop residues, and animal dung cakes burnt for cooking or heating, is also extremely important. Three billion people are exposed to biomass smoke and worldwide it is responsible for about 35% of cases of COPD. To underline its importance, in 2010 the three leading contributors to global disease burden expressed as disability adjusted life years were high blood pressure (7.0% [95%

uncertainty interval 6.2–7.7] of DALYs), tobacco smoking including second-hand smoke (6.3% [5.5–7.0]), and household air pollution from solid fuels (4.3% [3.4–5.3]). Exposure to outdoor air pollution also contributes to impaired lung development, the development of COPD, and exacerbation of COPD symptoms.

Illicit drug use is a risk factor, including inhaled marijuana but also heroin and crack cocaine.

Occupation

COPD is more common in people exposed to dust, fumes, or chemicals through their occupation. Confirmation of these links for specific occupations can be confounded by the effects of smoking and depends on accurate data about exposure over time. In the United Kingdom, evidence for an association between coal dust exposure and the development of COPD has led to the establishment of COPD as a disease that is considered for compensation in miners. Exposure to welding fumes has been shown to be associated with the development of COPD in a study of shipyard workers, and workers exposed to cadmium have an increased risk of emphysema. More recently it has been recognized that exposure to products used in cleaning work also increases the risk of COPD.

Diet

Undernutrition in childhood can impact on lung development and thus increase the risk of COPD in later life. Data on specific dietary components is less clear. There is some evidence that low vitamin D levels may accentuate the effects of smoking on the lung and they have been found to be associated with lung function impairment, though there are potential problems with reverse causation. Several studies have reported associations between frequent or high consumption of cured meats and increased risk of developing COPD.

Gender

Although historically COPD had a male preponderance, there has been a rapid increase in the prevalence, morbidity, and mortality of COPD in women, largely due to increases in their tobacco consumption. There is evidence that women may be more susceptible to the effects of inhaling smoke and that they are more likely to develop a chronic bronchitis phenotype. The factors underlying this remain to be established.

Airway hyperresponsiveness and asthma

The relationship between asthma and COPD is complex. Traditional descriptions have stressed clearly defined differences between the two conditions. However, it is now clear that both diagnostic terms encompass a range of phenotypes and shared pathologies and that these may overlap and evolve over an individual's lifetime. Bronchial hyperactivity in childhood

as well as a diagnosis of asthma are both powerful predictors of the presence of COPD in later life. This may in part be because chronic inflammation in asthma eventually causes reversible airway obstruction to become fixed, but there is also an increased risk of smokers with asthma developing emphysema, suggesting some common or synergistic inflammatory pathways in the two conditions. Studies in middle-aged smokers with a degree of impairment of lung function show a positive correlation between accelerated decline in FEV₁ and increased airway responsiveness to either methacholine or histamine.

Epidemiology

Prevalence

The prevalence of COPD increases with age. Data from the Burden of Lung Disease study (Fig. 18.8.3) suggest that about 10% of individuals over the age of 40 have COPD; 10.1% (SE 4.8) overall, 11.8% (7.9) for men, and 8.5% (5.8) for women. It is now the third leading cause of death worldwide, a position achieved partly through smoking habits and partly as a consequence of increased life expectancy as other cause of death such as communicable diseases become less prevalent. In environments with high biomass smoke exposure, COPD can be more prevalent at younger ages. For example, the FRESH AIR study in rural Uganda found that in people aged 30–39 years, 38% of men and 40% of women had COPD.

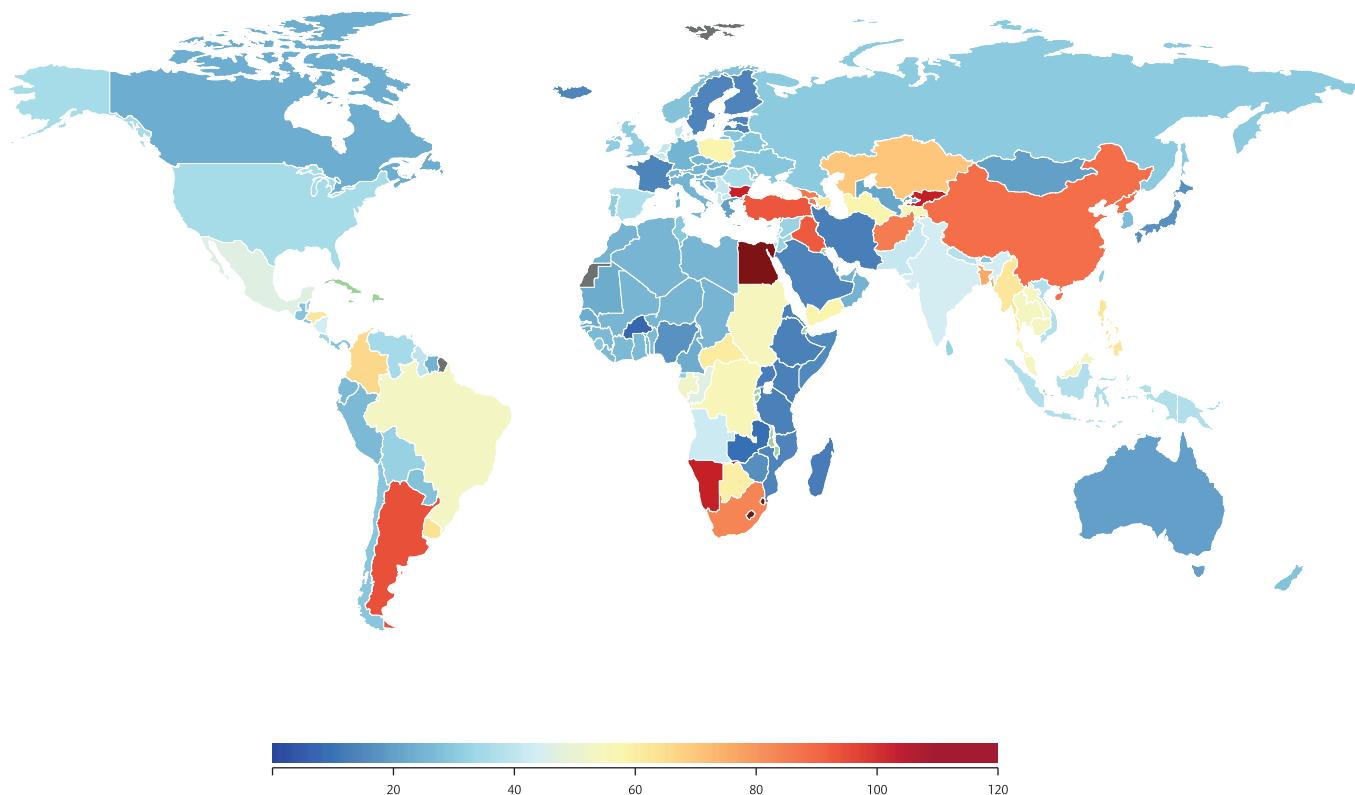


Fig. 18.8.3 Global age-standardized mortality rate for COPD.

Institute for Health Metrics and Evaluation (IHME). COD Visualization. Seattle, WA: IHME, University of Washington, 2014. Available from <http://ihmeuw.org/3r9k> (accessed 2nd June 2015).

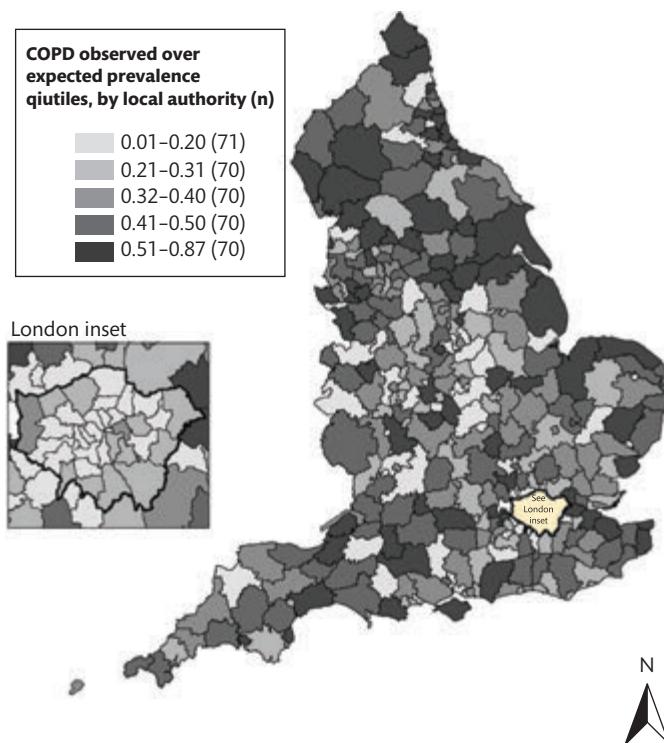


Fig. 18.8.4 Diagnosed vs. estimated COPD prevalence by Local Authority area in England Heat map compares expected and observed prevalence of COPD. Darker colours indicate that a higher proportion of cases have been identified.

From Nacul L, et al. (2011). COPD in England: a comparison of expected, model-based prevalence and observed prevalence from general practice data. *J Public Health (Oxf)*, 33(1), 108–16, by permission of Oxford University Press.

There is a marked disparity between the prevalence of diagnosed COPD and that predicted from epidemiological surveys. For example, the diagnosed prevalence of COPD in England in 2011 was 765 000 compared to an expected prevalence of 1.4 million (Fig. 18.8.4). This underdiagnosis is likely to reflect normalization of symptoms, where patients attribute breathlessness to normal ageing and dismiss cough and sputum production as normal. In addition, there is evidence that numerous opportunities to make the diagnosis of COPD are missed in primary care before it is finally

Table 18.8.2 Classification of the severity of airflow limitation in COPD (based on post-bronchodilator spirometry)

COPD stage	FEV ₁ (In patients with FEV ₁ /FVC <0.70 or <5th percentile)
Stage 1: Mild	≥80% predicted
Stage 2: Moderate	50–79% predicted
Stage 3: Severe	30–49% predicted
Stage 4: Very severe	<30% predicted

identified. In the 2014 Royal College of Physicians (RCP)/British Thoracic Society (BTS) COPD audit of 13 414 patients admitted to hospital with an acute exacerbation of COPD (AECOPD), 7% had no prior diagnosis of the condition.

Prevalence also depends on the spirometric definition chosen. Airflow obstruction is the characteristic feature of COPD and a ratio of FEV₁/VC less than 70% has been adopted in most national and international guidelines, and severity of disease can be classified according to the severity of airflow limitation (Table 18.8.2). Because lung elasticity declines with age the FEV₁/VC ratio tends to fall in healthy individuals, which means that a fixed ratio definition tends to underestimate the prevalence of COPD in younger people and overestimate it in older individuals. Having a variable lower limit of normal has been proposed as a more accurate approach. For epidemiological studies this is important, but for diagnosis in an individual presenting with symptoms it is less so, and the added complexity of a variable vs. fixed ratio means that the latter is preferred. In addition, evidence suggests that mild airflow obstruction (an FEV₁ between 80 and 100% predicted) in the absence of symptoms of cough sputum or breathlessness does not predict the development of subsequent lung disease.

Mortality

COPD has become, based on data from the 2010 Global Burden of Disease study, the third leading cause of death worldwide (after stroke and ischaemic heart disease) and the ninth leading cause of life years lost (Fig. 18.8.5). This is due in large part to increased longevity, which increases the impact of diseases that

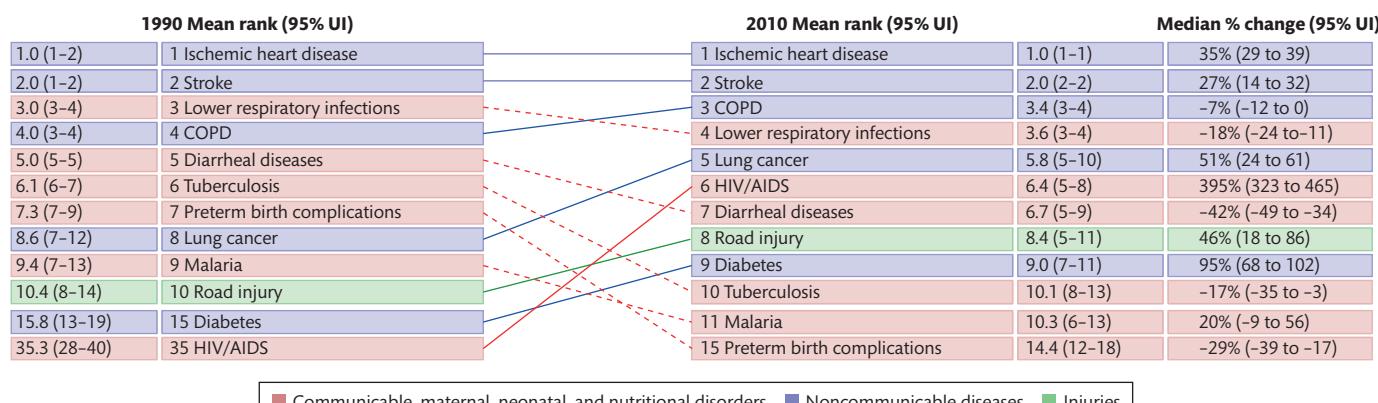


Fig. 18.8.5 Global causes of death 1990 to 2010.

Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, 2013. Available from <http://vizhub.healthdata.org/irank/arrow.php>. (accessed 5th June 2015).

occur in older age, combined with changes in smoking habits. In the European Union and in what is defined as the 'developed world', it is the fourth leading cause of death (after lung cancer as well). It is fifth in North America (where Alzheimer's disease is also a more common cause of death; see Fig. 18.8.6). Mortality rates have fallen in men but risen in women, reflecting later smoking uptake in women.

There is a strong association between COPD mortality and deprivation, which is not completely explained by smoking habits (Fig. 18.8.7). Possible explanations include persisting effects of early life disadvantage, greater exposure to pollution, fuel poverty (meaning poorer individuals are more likely to live in cold damp homes), as well as difficulties in accessing healthcare, particularly in healthcare systems where access is based on ability to pay.

Prevention

COPD is preventable, but its prevention requires political will to implement tobacco control measures fully. Smoking is an addiction that usually starts in childhood and is predicted to kill one billion people in the 21st century. The global social burden is estimated to be \$2.1 trillion a year. The means to prevent this harm are set out clearly in the World Health Organization's 2003 Framework Convention on Tobacco Control and the associated MPOWER policy framework (Monitor tobacco use and prevention policies, Protect people from tobacco smoke, Offer help to quit tobacco use, Warn about the dangers of tobacco, Enforce bans on tobacco advertising, promotion, and sponsorship, and Raise taxes on tobacco). Countries that have implemented these measures most comprehensively and effectively have seen the greatest falls in smoking rates. Further actions are suggested in the 2015 report from Action on Smoking and Health (ASH) 'Smoking still kills'. In particular, prevention needs to focus on specific groups where smoking remains high. These include those in poverty, people with mental illness, the homeless, prisoners (the smoking

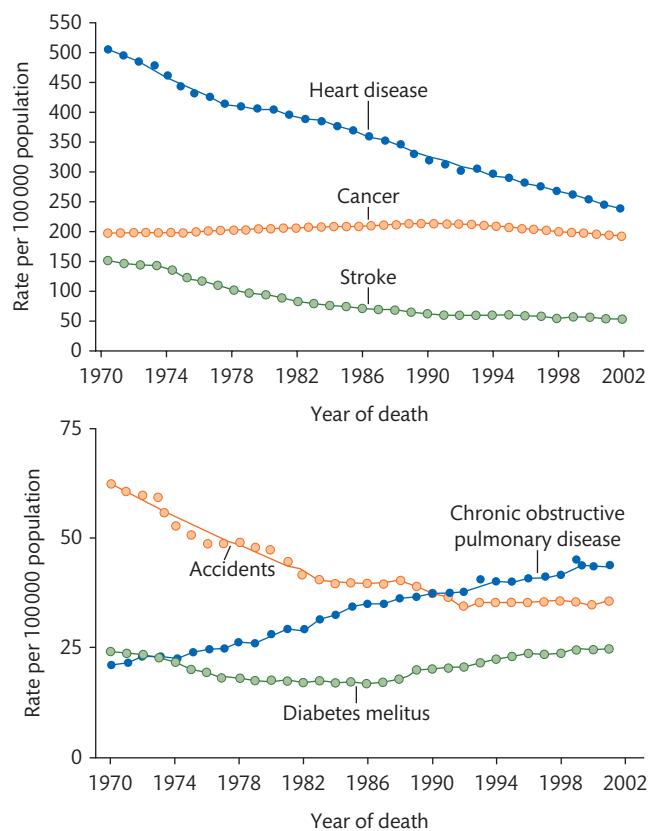


Fig. 18.8.6 US trends in age-standardized death rates for the six leading causes of death in the United States.

From Jemal, et al. *JAMA* 2005; 294: 1255–9. Copyright © 2005, American Medical Association. All Rights reserved.

rate for inmates in the United Kingdom is 80%) and the LGBT community.

Ensuring every child has a good start in life, one of the principles from the 2010 Marmot Review 'Fair Society, Healthy Lives' includes

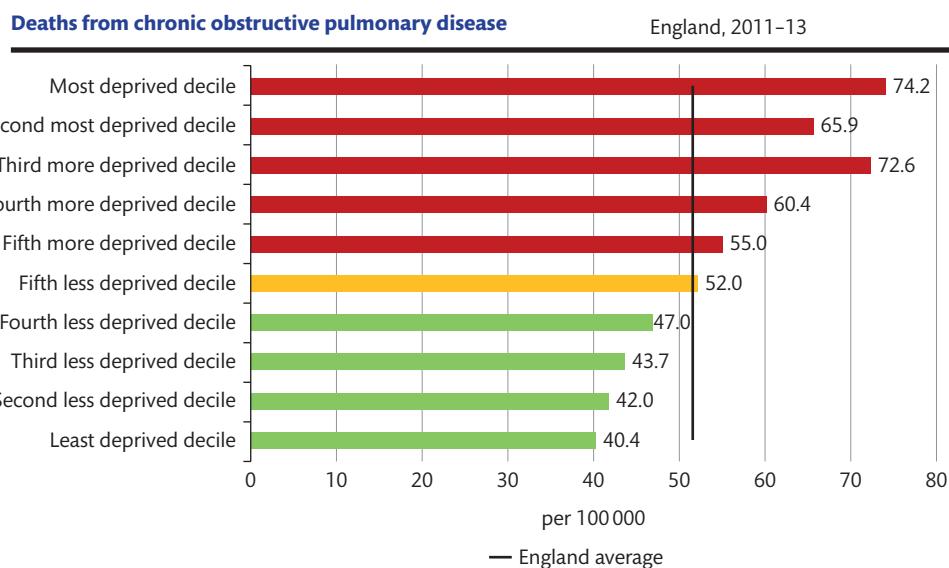


Fig. 18.8.7 Mortality rates for COPD in England by decile of deprivation.

Available from Public Health England, <http://www.tobaccoprofiles.info/profile/tobacco-control/data#gid/1000110/pat/6/ati/101/page/1/par/E12000007/are/E0900002> (accessed 3rd June 2015).

ensuring healthy lung development both *in utero* and subsequently, as well as action to reduce inequalities, improve nutrition, and reduce exposure to biomass smoke.

Pathology

COPD occurs as a result of a range of pathological mechanisms occurring in response to inhaled material. Principal among these are inflammation, oxidative stress, and proteolysis. Autoimmune processes may also be involved as well as accelerated senescence and cell death. Effects include destruction and remodelling of lung tissues with impacts at the alveolar, small, and large airway level. The pulmonary vasculature is also damaged which can lead to secondary impacts on the heart. Systemic effects of COPD are common and can be difficult to distinguish from comorbidities, which are the norm rather than the exception in COPD. Key pathological features are outlined in Table 18.8.3.

Chronic bronchitis

The pathological basis of the hypersecretion of mucus in chronic bronchitis is an increase in the volume of the submucosal glands, and an increase in the number and a change in the distribution of goblet cells in the surface epithelium (Fig. 18.8.8). Submucosal mucus glands are confined to the bronchi, decreasing in number and in size in the smaller, more peripheral bronchi, and are not present

in the bronchioles. In chronic bronchitis, there is mucus gland hypertrophy in the larger bronchi with infiltration of the glands with inflammatory cells.

In healthy subjects who have never smoked, goblet cells are predominantly seen in the proximal airways and decrease in number in more distal airways, being absent normally in the terminal or respiratory bronchioles. By contrast, in smokers, goblet cells not only increase in number but mucus metaplasia means that they extend more peripherally, hence mucus is produced in greater quantities in peripheral airways where the mucociliary escalator is less developed.

Mucociliary function is also decreased in smokers. Mucus concentration changes with a greater proportion of solid material, making it harder to clear via the muco-ciliary escalator. Cigarette smoke has also been shown to produce cilia shortening and ciliophagy, impairing mucus clearance.

Bronchial biopsies in patients with chronic bronchitis reveal that activated T lymphocytes are prominent in the proximal airway walls. However, in contrast to asthma, macrophages also feature, and the CD8 suppressor T-lymphocyte subset (rather than CD4) predominates (Table 18.8.4). Increased numbers of neutrophils are present, particularly in the glands, which become even more prominent as the disease progresses. Bronchial biopsies from limited studies in patients during exacerbations of chronic bronchitis show increased numbers of eosinophils in the bronchial walls, although their numbers are small compared with exacerbations of asthma

Table 18.8.3 Pathological changes in COPD

Proximal airways (trachea and cartilaginous airways >2 mm diameter)
Submucosal bronchial gland enlargement, glands, and goblet cell metaplasia—resulting in excessive mucus production or chronic bronchitis; cellular infiltrates (neutrophils, lymphocytes) also occur in bronchial glands
Increased macrophages, CD8 + T lymphocytes (cytotoxic T cells); few neutrophils or eosinophils, but neutrophils increase as the disease progresses
Airway wall changes include squamous metaplasia of the airway epithelium, ciliary dysfunction, and increased smooth muscle and connective tissue
Peripheral airways (noncartilaginous airways <2 mm internal diameter)
Bronchiolitis is present at an early stage of the disease. Luminal and inflammatory exudates that are increased in inflammatory response; exudates correlate with the disease severity
Pathological extension of goblet cells and squamous metaplasia in peripheral airways
Increased macrophages, T lymphocytes, CD8 + > CD4+, increased B lymphocytes, lymphoid follicles, fibroblasts; few neutrophils or eosinophils
Peribronchial fibrosis and airways narrowing as the disease progresses
Parenchyma (respiratory bronchioles and alveoli)
Emphysema-defined as abnormal enlargement of air spaces distal to terminal bronchioles
Alveolar wall destruction, apoptosis of epithelial and endothelial cells
Centrilobular emphysema—dilatation and destruction of respiratory bronchioles; commonly seen in smokers; predominant in upper zones
Panacinar emphysema—destruction of the whole of the acinus; commonly seen in α1-antitrypsin deficiency; more common in the lower lung zones
Microscopic emphysema in the early stages of the disease, progressing to macroscopic lesions or bullae (defined as an emphysematous space >1 cm diameter)
Increased macrophages, CD8 + T lymphocytes
Pulmonary vasculature
Increased thickening of the intima; endothelial dysfunction early in the course of the disease
Increased vascular smooth muscle occurs later
Increased macrophages and T lymphocytes
Collagen deposition, emphysematous destruction of the capillary bed, in later stages
Structural changes can eventually lead to pulmonary hypertension and right ventricular dysfunction (cor pulmonale)

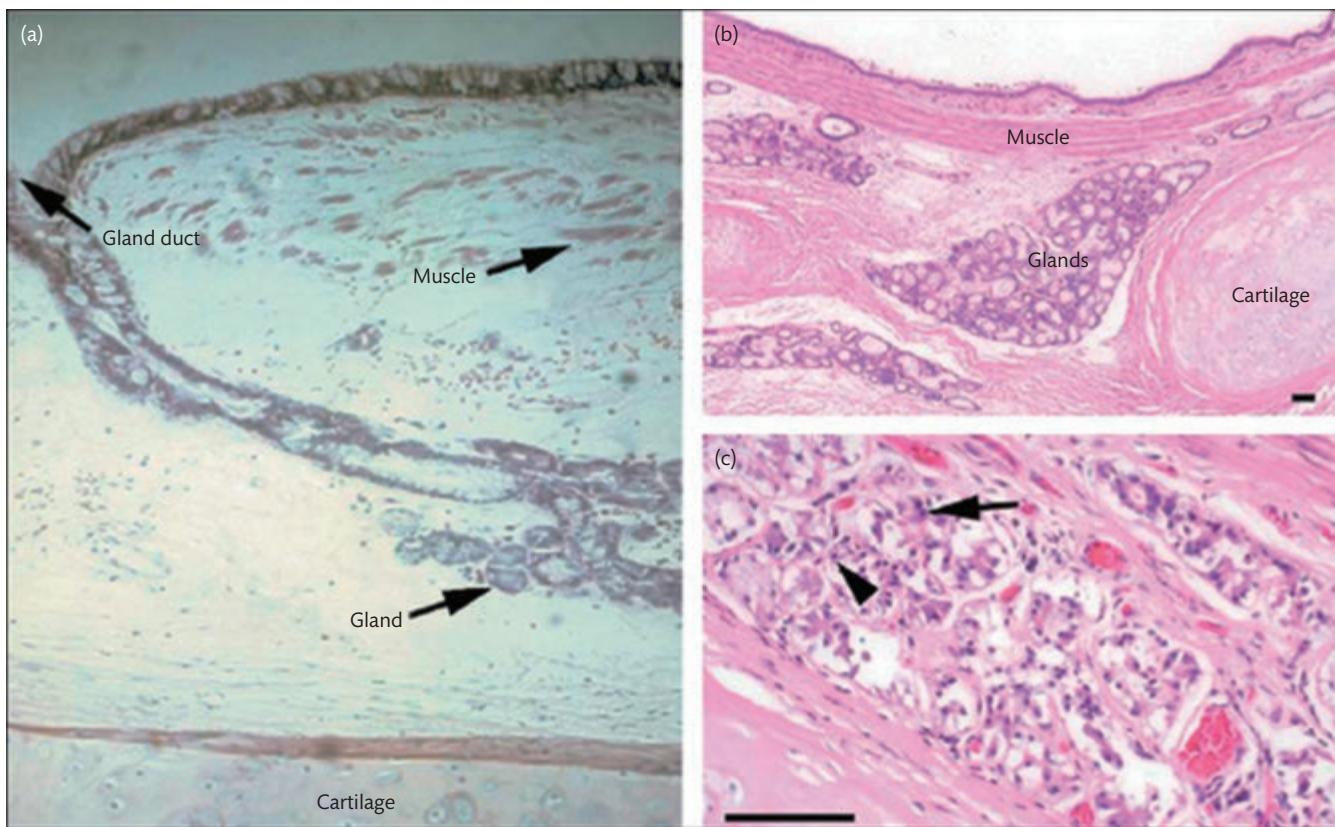


Fig. 18.8.8 A central bronchus from the lungs of a cigarette smoker with normal lung function (a) shows small amounts of muscle present in subepithelium and small epithelial glands. In a patient with chronic bronchitis (b) the muscle appears as a thick bundle and the bronchial glands are enlarged. At a higher magnification (c) these glands show evidence of a chronic inflammatory process involving polymorphonuclear leucocytes (arrow head) and mononuclear cells, including plasma cells (arrow).

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and—unlike those in asthma—these cells do not appear to have degranulated.

Patients with chronic bronchitis have increased intraluminal and air space inflammation, with or without airways obstruction, with predominantly neutrophils and macrophages in the bronchoalveolar lavage studies. There is also evidence that air space inflammation in patients with chronic bronchitis continues following smoking cessation if the production of sputum persists.

Table 18.8.4 Inflammatory cells in COPD

Neutrophils—increase in sputum and distal air spaces in smokers, with a further increase in COPD related to disease severity. These are important in the secretion and release of proteases

Macrophages—increase in number in airways, lung parenchyma, and in bronchoalveolar lavage fluid. These produce increased inflammatory mediators and proteases

T lymphocytes—increase in the peripheral airways and within lymphoid follicles, possibly as a response to chronic infection of the airways. Both CD4 and CD8 cells increase in airways and in lung parenchyma, with an increase in CD8:CD4 ratio. There is an increase in TH1 and TC1 cells that produce interferon- γ . CD8 + cells may be cytotoxic, causing alveolar wall destruction

Eosinophils—increase in airways walls, with increased eosinophil proteins in sputum, in some exacerbations of the disease

Emphysema

Emphysema is defined as enlargement of the airways distal to the terminal bronchioles, due to destruction of their walls without obvious fibrosis. Three major types are recognized, according to the distribution of enlarged air spaces within the acinar unit (Fig. 18.8.9), the acinus being that part of the lung parenchyma supplied by a single terminal bronchiole:

- Centriacinar (or centrilobular) emphysema, in which enlarged air spaces are initially clustered around the terminal bronchiole.
- Panacinar (or panlobular) emphysema, where the enlarged air spaces are distributed throughout the acinar unit.
- Paraseptal (paralobular or distal acinar) emphysema describes enlarged air spaces along the edge of the acinar unit, but only where it abuts against a fixed structure such as the pleura or a vessel.

Centrilobular emphysema is more common in the upper zones of the lung and is the common type in COPD. Panlobular emphysema may be found anywhere in the lungs, but is more prominent at the bases, and is the typical pattern associated with α_1 -antitrypsin deficiency. The different types of emphysema can occur alone or in combination in a patient with COPD. There is still debate over whether centrilobular and panlobular emphysema represent different disease processes, and hence have different

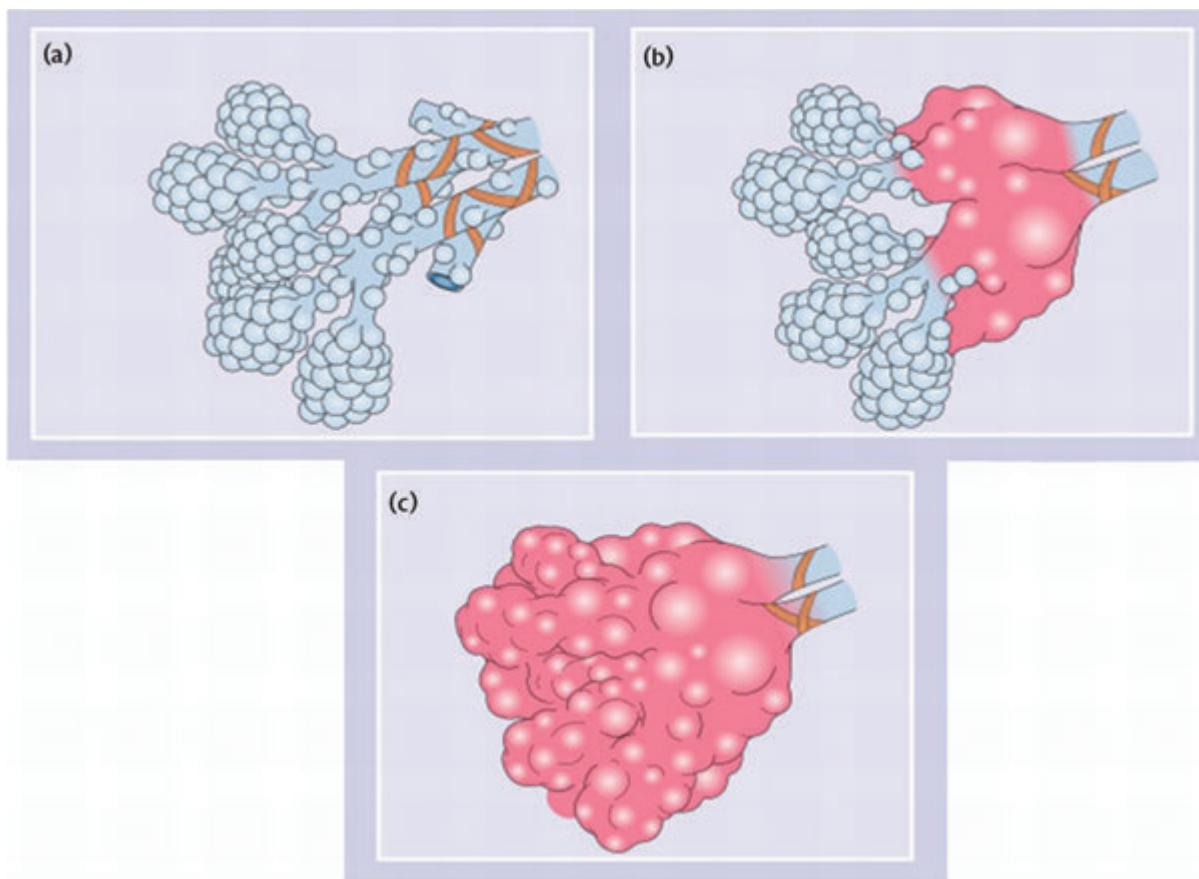


Fig. 18.8.9 Patterns of emphysema. (a) Normal respiratory bronchiole and alveolar structure. (b) Centrilobular emphysema. (c) Pan lobular emphysema.

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aetiologies, or whether panlobular emphysema is a progression from centrilobular emphysema. Cigarette smoking has a clearer association with centrilobular emphysema than with panlobular emphysema. Smokers with centrilobular emphysema have more small airways disease than those patients with predominantly panlobular emphysema.

In the early stages of the disease, emphysematous lesions are microscopic (<1 mm diameter); they may progress to macroscopic lesions or bullae. Bullae are conventionally considered to be areas of emphysema that is distended to more than 1 cm in size. Bullous disease can also occur in the absence of COPD.

Normal bronchioles and small bronchi are supported by attachments to the outer aspect of their walls of adjacent alveolar walls, an arrangement which maintains the tubular integrity of the airways. Loss of these attachments in emphysema leads to loss of the elastic recoil of the lungs and hence distortion and irregularity of airways, which results in airflow limitation (Fig. 18.8.10).

The inflammatory cell profile in the alveolar walls and the air spaces is similar to that described in the airways and persists throughout the course of the disease, even after smoking cessation. Although absence of fibrosis is a prerequisite in the most recent definition of emphysema, fibrosis does occur in the terminal or respiratory bronchioles as part of a respiratory bronchiolitis in COPD patients. Furthermore, there is an increase

in collagen in the lung parenchyma in smokers compared with nonsmokers.

Bronchiolitis/small airways disease

Increased flow resistance in the lungs in patients with COPD largely occurs in the small airways (<2 mm diameter) at the periphery of the lungs. This was demonstrated mathematically in 1965 by Malcolm Green and directly measured in 1968 by Hogg, Macklem, and Thurlbeck in studies using a retrograde catheter. Inflammation in the small airways is among the earliest changes to be found in asymptomatic cigarette smokers and considerable changes in these airways can occur without giving rise to symptoms or alterations in spirometry. Several pathological changes are found in small airways (Fig. 18.8.11), including inflammatory infiltrate in the airway wall, mucus and cells in the lumen, goblet cell hyperplasia, fibrosis in the airway wall, squamous-cell metaplasia, mucosal ulceration, increased amount of muscle, and pigmentation.

Bronchiolitis is present in the peripheral airways at an early stage of the disease. The inflammatory cells in the airway wall and air spaces are similar to those in the larger airways. Studies using resected lung specimens, and those obtained during lung volume reduction surgery, have shown changes in inflammatory response as the disease progresses which are thought to represent innate and adaptive immune responses to long-term exposure to noxious particles and gases.

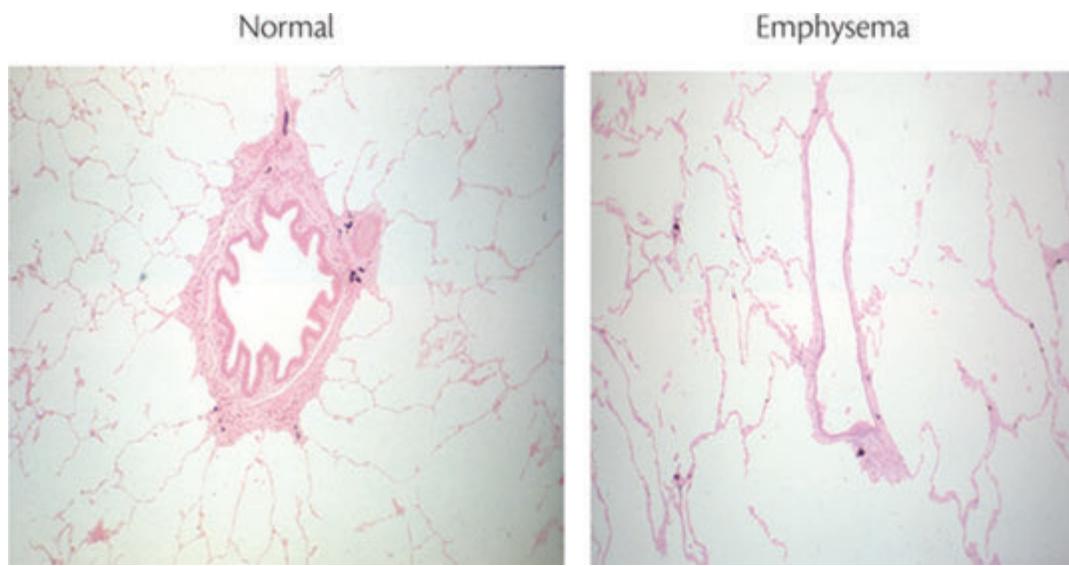


Fig. 18.8.10 Pathological changes in emphysema. Cross-section of a normal small peripheral bronchiole, showing a circular outline supported by adjacent alveolar walls (left panel). A small bronchiole at the same magnification in a patient with very early macroscopic emphysema: the loss of alveolar supporting walls results in an elliptical airway (right panel).

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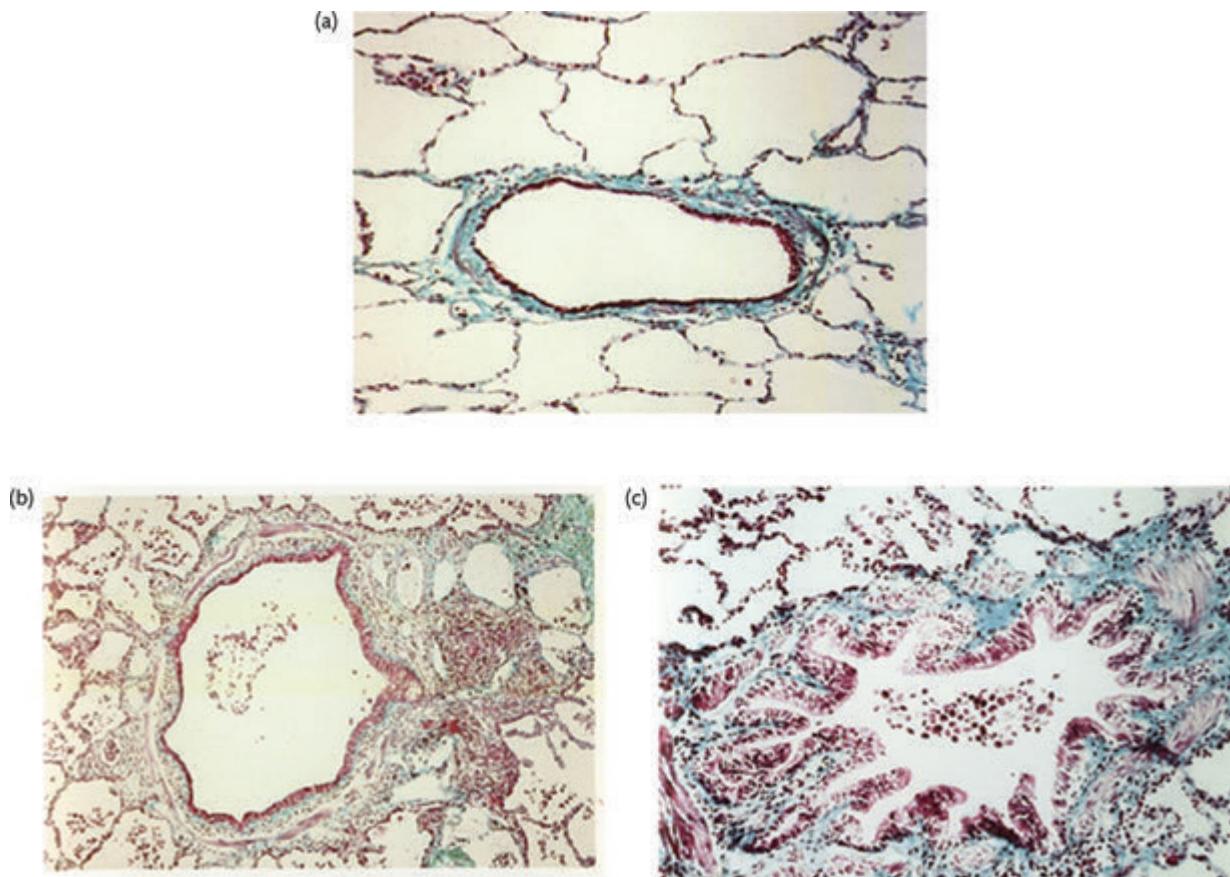


Fig. 18.8.11 Histological sections of peripheral airways. (a) Section from a cigarette smoker with normal lung function, showing a nearly normal airway with some inflammatory cells in the airway wall. (b) Section from a patient with small airways disease, showing inflammatory cells in the wall and inflammatory exudate in the lumen of the airway. (c) A more advanced case of small airways disease, with narrowed lumen, structural reorganization of the airway wall, increased smooth muscle, and deposition of peribronchiolar connective tissue.

Images reproduced with the kind permission of Professor James C. Hogg, University of British Columbia.

Recent work, using micro CT, has shown that loss of terminal bronchioles precedes the development of emphysema, highlighting the importance of the small airways. This approach has also allowed linkage of pathological processes to macroscopic structure. Genes increasing in expression with increasing emphysematous destruction included those involved in inflammation, such as the B-cell receptor signalling pathway, while genes decreasing in expression were involved in tissue repair processes, including the transforming growth factor β (TGF β) pathway, actin organization, and integrin signalling.

A further feature in the later stages of the disease is the presence of an increase in B lymphocytes and lymphoid follicles around the bronchioles. The cause of these changes is not known, but it is possible that they represent an autoimmune or adaptive immune response to chronic lower respiratory infection. As the disease progresses there is fibrosis and increased deposition of collagen in the small airway wall.

Pulmonary vasculature

Pathological changes in the pulmonary vasculature occur early in the course of the disease. The initial changes are characterized by thickening of the vessel wall and endothelial dysfunction. These are followed by increased vascular smooth muscle and infiltration of the vessel walls by inflammatory cells, including macrophages and CD8 + lymphocytes. In the later stages of the disease there is collagen deposition and emphysematous destruction of the capillary bed in the alveolar walls. These structural changes can eventually lead to pulmonary hypertension and right ventricular dysfunction (cor pulmonale).

Pathogenesis

Inflammation is present in the lungs of all smokers, and amplification of this is a major factor in the development of COPD. The precise mechanisms of this amplification are not well understood, but the abnormal inflammatory response in COPD leads to increased tissue destruction, impairment of defence mechanisms that limit such destruction, and impairment of the repair mechanisms. In general, the inflammatory and structural changes in the airways increase with disease severity and persist even after smoking cessation. However, in addition to inflammation, other processes are involved in the pathogenesis of COPD:

- Imbalance between proteases and antiproteases
- Imbalance between oxidants and antioxidants (oxidative stress)
- Immune dysfunction and impaired bacterial clearance
- Fibrosis or disordered lung remodelling in small airways
- Accelerated senescence and cell death
- Mitochondrial dysfunction and mitophagy

These processes interact through a range of mechanisms (Fig. 18.8.12), so their division into categories is somewhat artificial.

Inflammatory cells and mediators

The inflammatory cellular response which characterizes COPD consists of increased numbers of neutrophils, macrophages, and T lymphocytes (CD8 more than CD4) in the lungs (Fig. 18.8.13). These inflammatory cells are activated to release a variety of cytokines

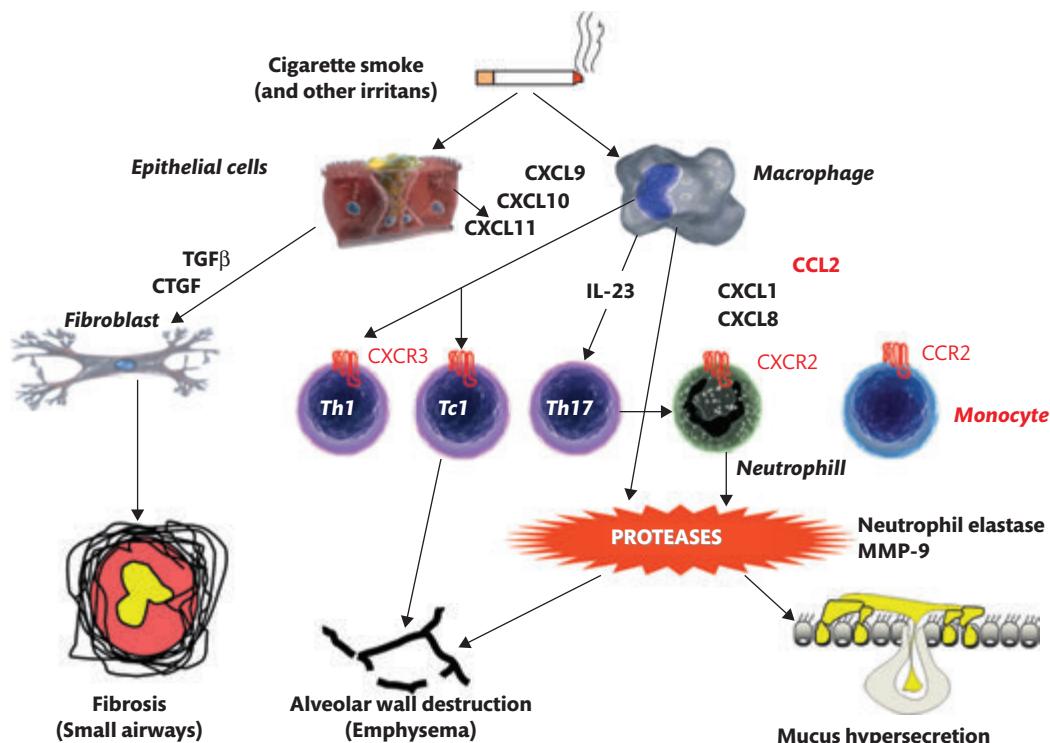


Fig. 18.8.12 Cigarette smoke—pathways of harm in COPD.

Image provided courtesy of Professor Peter Barnes, Imperial College London.

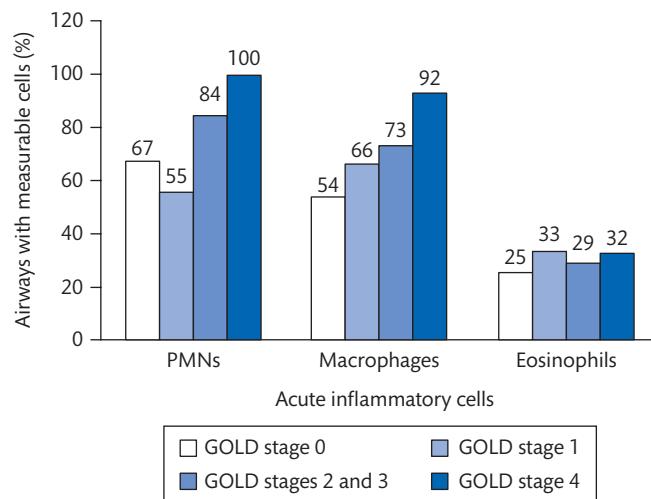


Fig. 18.8.13 The extent of the airway inflammatory response, as measured by the percentage of the airways containing CD4 cells, CD8 cells, and B cells, among patients in each GOLD stage of COPD.

Reproduced from Hogg JC, et al. (2004). The nature of small-airway obstruction in chronic obstructive pulmonary disease. *New England Journal of Medicine*, **350**(26), 2645–53. Copyright © 2004 Massachusetts Medical Society.

and mediators, by bacteria and in response to apoptotic cells leading to airway damage which promotes persistent colonization in a positive feedback loop. A wide range of inflammatory mediators have been shown to be increased in COPD and to amplify the inflammatory process (Table 18.8.5).

Protease/antiprotease imbalance

Important to understanding the pathogenesis of COPD were the observations of an association between α_1 -antitrypsin deficiency and the development of early-onset emphysema, and the development of emphysema following instillation of the proteolytic enzyme papain into rat lungs. These observations form the basis of the protease/antiprotease hypothesis of the pathogenesis of emphysema, which states that under normal circumstances the release of proteolytic enzymes from inflammatory cells that migrate to the lungs to fight infection does not cause lung damage because of inactivation of these proteolytic enzymes by an excess of inhibitors. However, in conditions of excessive enzyme load, or where there is an absolute or a functional deficiency of antiproteases, an imbalance develops between proteases and antiproteases in favour of proteases, leading to uncontrolled enzyme activity and degradation of lung connective tissue such as elastin in alveolar walls, resulting in emphysema.

Table 18.8.5 Inflammatory mediators in COPD

Leukotriene B ₄ —a neutrophil and T-cell chemoattractant that is produced by macrophages, neutrophils, and epithelial cells
Chemotactic factors—e.g. the CXC chemokines IL-8 and growth-related oncogene α —produced by macrophages and epithelial cells; attract cells from the circulation and amplify proinflammatory responses
Proinflammatory cytokines—e.g. TNF α , IL-1 β , IL-
Growth factors—e.g. TGF β —which may cause fibrosis in the airways either directly or through release of another cytokine, connective tissue growth factor

Oxidative stress

The oxidative burden is increased in COPD as a result of oxidants from cigarette smoke and reactive oxygen and nitrogen species released from inflammatory cells. There may also be a reduction in endogenous antioxidant responses due to a reduction in the transcription factor Nrf2 that regulates many antioxidant genes. Both factors contribute to oxidant–antioxidant imbalance and hence oxidative stress, many markers of which are increased in stable COPD and further increased during acute exacerbations. Oxidative stress can lead to inactivation of antiproteases, stimulation of mucus production, and activation of proinflammatory genes. Amplification of inflammation can result from oxidative stress enhanced transcription factor activation (such as NF- κ B) by oxidants, and may also result from a decrease in histone deacetylase activity in lung cells of patients with COPD with consequent increased gene expression of inflammatory mediators. Oxidative stress-induced mitochondrial dysfunction appears to be an important driver of inflammation and airway smooth muscle remodelling in patients with chronic obstructive pulmonary disease.

Immune dysfunction

The fact that inflammation persists in people with COPD after they quit smoking has raised the question of what sustains the process. The persistence of bacterial colonization in COPD patients suggests impaired immune function, with evidence that this involves both the innate and acquired immune responses. Bacterial clearance by macrophages is impaired in COPD, which perpetuates the inflammatory response. Neutrophils are also aberrant, with increased survival and motility, but lack direction which could lead to more widespread destruction during migration.

Accelerated ageing

Lung function decrease is a feature of normal ageing. A gradual loss of lung elasticity leads to age-related decline in FEV₁. Additional processes in COPD include destruction of the alveolar walls and fibrosis of peripheral airways, but it is increasingly recognized that people with COPD display a range of exaggerated ageing-associated processes, including an increase in cellular senescence, stem cell exhaustion, mitochondrial dysfunction contributing to increased oxidative stress, defective autophagy, alteration in the extracellular matrix, and a reduction in endogenous antiageing molecules such as sirtuins.

Pathophysiology

Airflow obstruction

Expiratory airflow obstruction is a cardinal feature of COPD (Fig. 18.8.14 and 18.8.15). Expiratory flow rate is lung volume dependent and depends on two factors: (1) the driving pressure produced by the respiratory muscles and elastic properties of the lungs and chest wall; (2) the resistance to airflow of the system. Airflow resistance increases during expiration as airways narrow and the elastic recoil of the lung falls. In COPD, resistance is increased by destruction of small airways as well as epithelial damage and mucus. This is further aggravated by loss of elastic airway attachments through emphysema. The latter process causes airways to

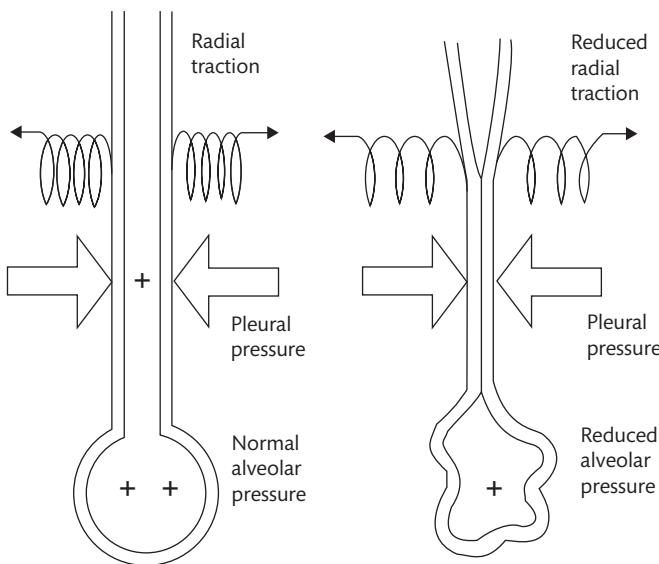


Fig. 18.8.14 Mechanisms of airflow limitation in COPD. The image on the left shows normal pattern with elastic recoil of the lung contributing to alveolar pressure and elastic attachments helping to pull airways open. On the right, reduction in these in COPD leads to airway closure.

narrow both by reducing radial traction which pulls airways open from outside and reduces the driving pressure within the airway itself. This leads to premature airway closure and gas trapping.

Lung volumes and hyperinflation

Lung volumes are increased in COPD because of two processes. The first is a change in the balance between the elastic recoil of the lung and the tendency of the chest wall to spring outwards. The point where these are matched determines functional residual capacity (FRC), which in health is the volume of air in the lung at the end of a quiet tidal breath. Emphysema makes lungs more compliant so that this point is higher leading to static hyperinflation (Fig. 18.8.16). The second process is that early airway closure, because of the mechanisms described here, means that expiration ends before the lungs have emptied.

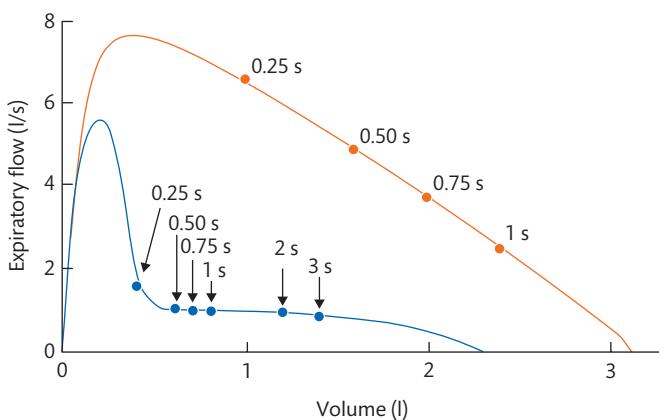


Fig. 18.8.15 Maximum flow volume curves in a healthy subject (FEV_1 2.4 litres) and a subject with COPD and airways obstruction (FEV_1 0.8 litres). The development of convexity of the expiratory curve in mild obstruction is characteristic, as is the relative preservation of peak expiratory flow in the patient with COPD. Timepoints in second(s) are plotted on the flow volume curves.

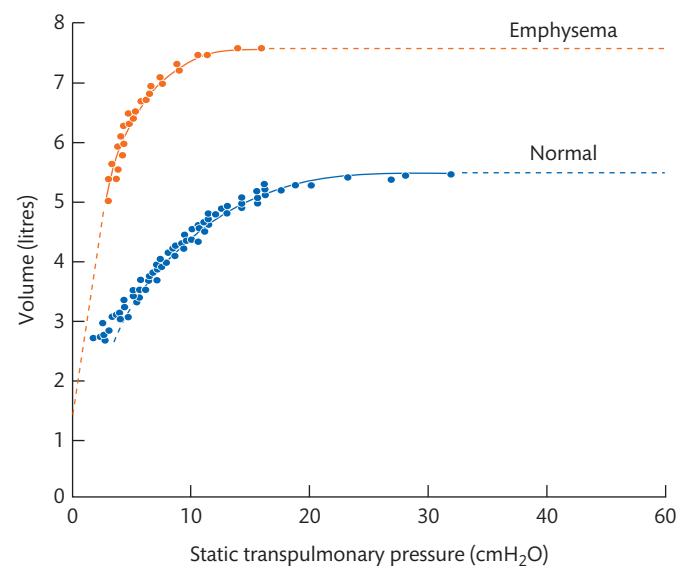


Fig. 18.8.16 Static expiratory pressure volume curves of lungs in a subject with severe emphysema compared with a normal subject. The broken lines represent extrapolation of the curve—to infinite pressure and to the volume axis at zero pressure.

In health, increased ventilatory requirements are met by increasing respiratory rate and tidal volume. In the presence of flow limitation it is necessary to increase operating lung volumes (Fig. 18.8.17). This process is called dynamic hyperinflation. Although this allows a higher flow rate (and therefore minute volume) it has several adverse consequences (Table 18.8.6 and Fig. 18.8.18). As lung volumes increase the load on the respiratory muscles increases and their capacity to meet this load decreases.

A key concept in dynamic hyperinflation is that because total lung capacity does not change, there is a limit to the increases in end

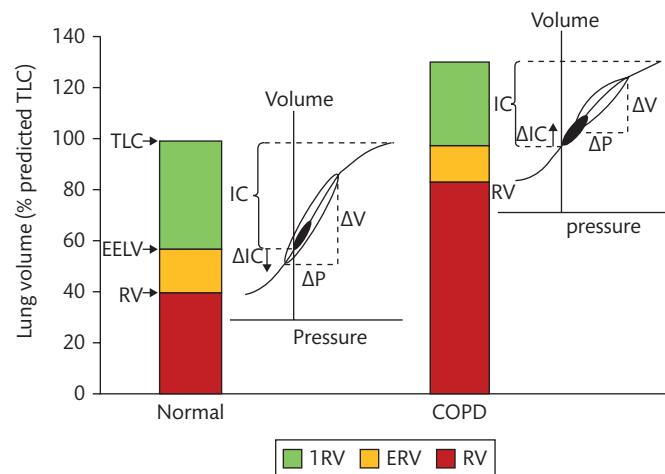


Fig. 18.8.17 Pressure volume curve of the lung in health and COPD. Reduced elastic recoil and airway closure leads to increased residual volume (RV), end expiratory lung volume (EELV) and total lung capacity (TLC). This impacts on inspiratory and expiratory reserve volume (IRV and ERV, respectively).

From Langer D, et al. (2014). Lung hyperinflation in chronic obstructive pulmonary disease: mechanisms, clinical implications and treatment. *Expert Review of Respiratory Medicine*, 8, 731–49.

Table 18.8.6 Consequences of dynamic hyperinflation

Increased load
The lungs move onto the upper, flatter part of the pressure volume curve increasing the work needed to expand them
At high volumes, tendency of chest is to recoil inwards creating additional threshold load
Early airway closure creates positive end expiratory pressure
Impaired capacity
The respiratory muscles become mechanically disadvantaged. The diaphragm is shortened and flattened, moving it away from the optimum length tension relationship for the muscle
Increased intrathoracic pressures and increased volume of the lungs impair cardiac function
Respiratory muscle 'steal'—blood flow is diverted away from limb muscles which may accelerate fatigue
Tidal volume constraint—total lung capacity cannot be increased so increased end expiratory lung volume is accompanied by a restriction in inspiratory reserve volume in turn constraining tidal volume (Fig. 18.8.18)

expiratory lung volume and tidal volume that can be accommodated. The O'Donnell Threshold describes the inspiratory reserve volume at which patients experience intolerable dyspnoea in the face of the ventilatory demand of exercise. It is this parameter, rather than the end expiratory lung volume (EELV) per se, which forms a limit to exercise capacity.

During acute exacerbations (Table 18.8.7) there is increased airway inflammation, mucus, and smooth muscle contraction, so airways become narrower or completely occluded. This increases flow limitation, driving an increase in operating lung volumes and breathlessness. Ventilation inequality increases meaning that ventilation is less efficient, which may cause hypoxia and hypercapnia.

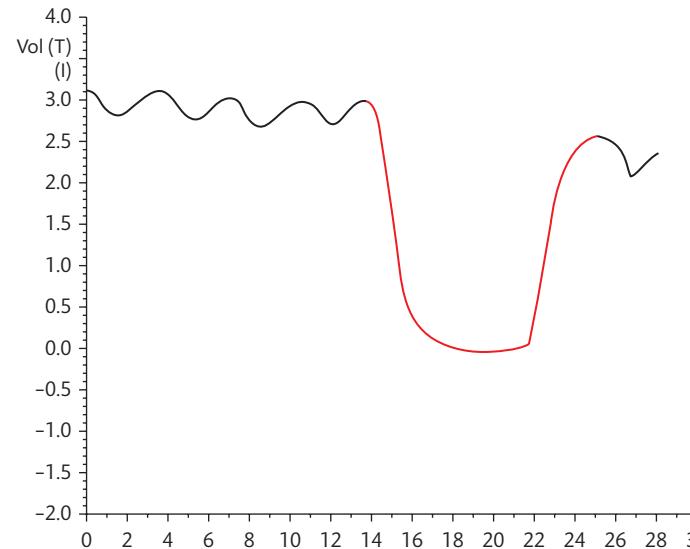


Fig. 18.8.18 Volume time curves at beginning and end exercise in COPD. The image on the left shows 30 seconds of quiet tidal breathing in a COPD patient at rest. Inspiratory flow is downwards and the red section represents an inspiratory capacity manoeuvre where the patient is asked to take a maximum breath in at the end of their next normal breath out. The image on the right shows the same manoeuvre at the end of exercise: respiratory rate and tidal volume have increased, and the inspiratory capacity (the amplitude of the red trace) is reduced, reflecting an increase in end expiratory lung volume.

Author's data.

Table 18.8.7 Mechanisms of impact of acute exacerbation of COPD

Inflammation and mucus narrow and occlude airways
Ventilation/perfusion matching impaired. Increased dead space
- hypoxia - hypercapnia
Increased airflow limitation leads to dynamic hyperinflation
- respiratory muscles less efficient - ventilation less efficient - cardiac function compromised - increased work of breathing
Increased lung volumes impair cardiac function
Systemic inflammatory mediators
Hypoxia and sympathetic activation drive fluids retention/oedema
Corticosteroids
- effects on skeletal muscle - metabolic derangement

Gas exchange

Gas exchange is impaired in COPD because of ventilation/perfusion inequality reflecting airway disease as well as alveolar and capillary bed destruction. Impaired cardiac output, due to hyperinflation as well as cardiac comorbidities, increases hypoxia as mixed venous oxygen saturations are lower. As COPD worsens there is also an increase in the proportion of each breath which is dead space ventilation, reducing ventilatory efficiency.

Respiratory muscles

Maximum inspiratory pressures are reduced in patients with COPD. The diaphragm is the main inspiratory muscle. At a microscopic level this shows evidence of a training effect, with an increase in slow twitch endurance fibres, but because lung hyperinflation causes the diaphragm to be shortened it is at a less favourable position on

Table 18.8.8 The MRC dyspnoea score

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on the level because of breathlessness, or has to stop to breath when walking at own pace
4	Stops for breath after walking about 100 m or after a few minutes on the level
5	Too breathless to leave the house, or breathless when dressing or undressing

the length tension curve, reducing its capacity to generate force. Adjusting for lung volume, diaphragm strength is normal in COPD. Flattening also reduces the zone of apposition, reducing the transmission of pressure to expand the lower ribcage. Accessory inspiratory muscles are also activated.

In health, expiration is passive at rest, relying on lung elastic recoil. In COPD the abdominal muscles are recruited to counter expiratory flow limitation. The diaphragm is relatively fatigue resistant in COPD patients, whereas the abdominal muscles have been shown to fatigue after maximal exercise. Abdominal muscle recruitment and increased intrathoracic pressures may impair cardiac output and may also cause or aggravate gastro-oesophageal reflux.

Limb muscles

Skeletal muscle impairment is present in about a third of people with COPD, assessed either in terms of reduced fat-free mass or in terms of lower limb strength. Upper limb muscles tend to be relatively well preserved, though patients often report difficulties with upper limb activities of daily living. This may in part be because shoulder muscles are used as accessory respiratory muscles. Hand strength is generally found to be preserved, particularly if nonvolitional tests are used to assess it.

The quadriceps muscle has been studied extensively in COPD. There is typically reduced bulk and a switch away from a slow twitch, endurance phenotype leading to reductions in both strength and endurance. The main cause of quadriceps impairment is physical inactivity, and these both occur early in COPD, not merely as 'end-stage' phenomena. Other proposed contributors to skeletal muscle impairment in COPD include systemic inflammation (though little inflammation has been observed in muscle biopsy samples), hypoxia, corticosteroids, and sympathetic activation.

COPD patients often have poor nutritional status, which can be reflected in muscle loss, and often have low levels of anabolic hormones. An inability to gain weight with nutritional supplementation is associated with a poor prognosis.

Clinical features

The key symptoms which should suggest the presence of COPD are breathlessness, cough, and sputum production occurring in an individual, usually over the age of 35, with a history of exposure to tobacco smoke or other noxious inhaled material. Physical activity limitation is often an early feature. Physical examination may be unremarkable in early disease, but as COPD becomes more advanced

signs of thoracic hyperinflation may appear. Objective evidence of airflow obstruction, obtained by spirometry, is essential for diagnosis.

Symptoms

Breathlessness on exertion is a cardinal symptom of COPD. The onset of breathlessness can be insidious and it is often misattributed to normal ageing. A typical history will describe several years of limitation and progressive avoidance of exertion (e.g. participation in leisure time activities and hobbies). Breathlessness at rest or in bed at night is unusual except in very severe disease and an additional explanation should be sought. Breathlessness in COPD is intertwined with fitness, because exertional breathlessness is a feature of lack of physical fitness and the two processes therefore interact. In addition, physical activity levels are reduced even in early COPD, with evidence linking physical inactivity with accelerated lung function decline. Anxiety symptoms can also modify or confuse presentation with breathlessness.

Breathlessness can be evaluated using instruments such as the Medical Research Council (MRC) dyspnoea score (**Table 18.8.8**) (a modified 'mMRC' score with similar categories but rated 0–4 instead of 1–5 is also commonly used). There is a strong association between breathlessness and health status as well as exercise capacity and survival in COPD, so it is incorporated into most composite staging systems.

Cough is also a frequent symptom of COPD. Cough occurs commonly in smokers and is a feature of bronchitis which may be present in the absence of airflow obstruction. The cough may be productive of sputum. Normalization of the symptom as a 'smoker's cough' may cause patients with COPD to delay presentation, leading to a later diagnosis at a more severe stage. Nocturnal cough does not appear to be increased in stable COPD. Paroxysms of coughing in the presence of severe airway obstruction generate high intrathoracic pressures, which can sometimes produce syncope and cough fractures of the ribs. Cough incontinence may also be a problem.

Wheeze may also occur due to turbulent airflow in large airways, but it is important to recognize that the absence of wheeze does not exclude a diagnosis of COPD.

Because of increased lung volumes, patients with COPD may experience chest tightness, particularly on exertion. Although expiratory rather than inspiratory airflow obstruction is the primary physiological impairment, high operating lung volumes mean patients frequently report a sensation of difficulty breathing in. Chest discomfort may also be present because of changes to the conformation of the ribcage and thoracic spine and in some individuals because of osteoporotic disease affecting the thoracic spine and ribs. A pleuritic pattern of pain suggests an additional diagnosis such as infection, pulmonary embolism, or a pneumothorax.

The most important symptoms associated with COPD have been formally established through the development of a patient-reported outcome tool, the COPD assessment test (CAT) score (**Fig. 18.8.19**). This includes eight questions answered 0–5, giving a total score 0–40 with increments of 10 representing mild (0–10), moderate (11–20), severe (21–30), and very severe (31–40) symptom burden. Routine assessment of health status in this way can help to ensure that important areas are covered and, as the measure can be used in any clinical setting (e.g. primary or secondary care and as an outcome measure for pulmonary rehabilitation), it is

Your name: _____ Today's date: _____

CAT
COPD Assessment Test™

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 1 2 3 4 5 I am very sad

Item	Score	Score Box
I never cough	0 1 2 3 4 5	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	
My chest does not feel tight at all	0 1 2 3 4 5	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	
I am not limited doing any activities at home	0 1 2 3 4 5	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	
I sleep soundly	0 1 2 3 4 5	
I have lots of energy	0 1 2 3 4 5	
		TOTAL SCORE

COPD Assessment Test and the CAT logo are trademarks of the GlaxoSmithKline group of companies.
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Fig. 18.8.19 The COPD assessment test score.

The COPD assessment test was developed by a multidisciplinary group of international experts in COPD supported by GSK. GSK activities with respect to the COPD Assessment Test are overseen by a governance board that includes independent external experts, one of whom chairs the board. COPD Assessment Test and the CAT logo is a trademark of the GlaxoSmithKline group of companies. It is available in more than 60 languages via <http://catestonline.org/> © 2009 GlaxoSmithKline. All rights reserved.

helpful for integrating care. Other health status measures include generic scores such as the SF-36 or respiratory specific tools such as the St George's Respiratory Questionnaire (SGRQ), the Clinical COPD questionnaire (CCQ), and the Chronic Respiratory Disease Questionnaire (CRDQ).

Physical activity limitation

Physical activity limitation is an important feature of COPD and one of the main symptomatic complaints. Although activity levels fall with increasing disease severity, it is also a feature of early disease

(Fig. 18.8.20), with reduction in step count seen even in GOLD stage I individuals. Physical activity is most strongly associated with measures of hyperinflation (Fig. 18.8.21).

The EU PROactive COPD project has developed a patient-reported outcome tool for assessing physical activity in COPD. Physical activity is influenced by both physical capacity and behavioural factors and is considered in two domains—difficulty with activities and amount of activities. The PROa tools incorporate both a questionnaire and direct physical activity monitoring to address the patient experience completely.

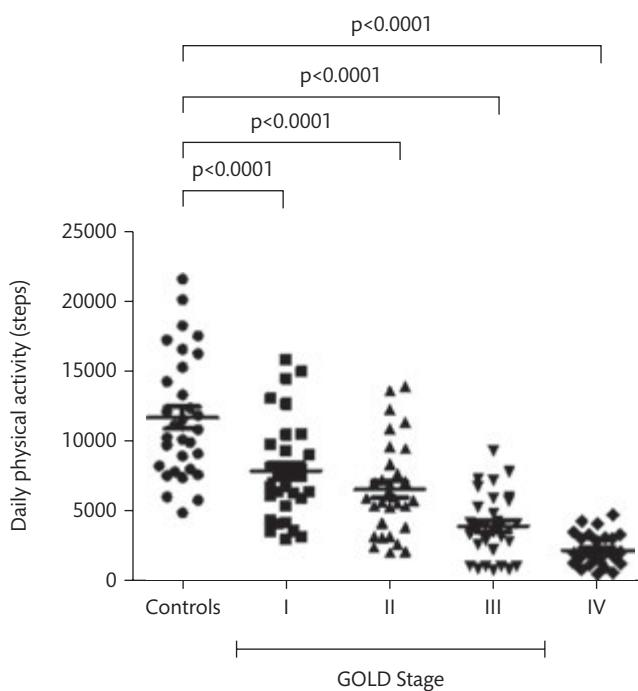


Fig. 18.8.20 Physical activity, assessed as step count using an accelerometer, decreases as COPD progresses, but is reduced even in early disease.

Figure courtesy of Dr Dinesh Shrikrishna.

Clinical questions and approach

When assessing a patient with COPD, the following considerations are of particular relevance:

- **Smoking history**—are they a current smoker? If not, when did they quit? What age did they have their first cigarette. Calculate pack per year smoke exposure. Is there any smoking of nontobacco drugs?
- **Effort intolerance can be assessed using the MRC dyspnoea scale.** In COPD there is usually only modest day to day variability. Do they do any regular exercise? Have they taken part in pulmonary rehabilitation?

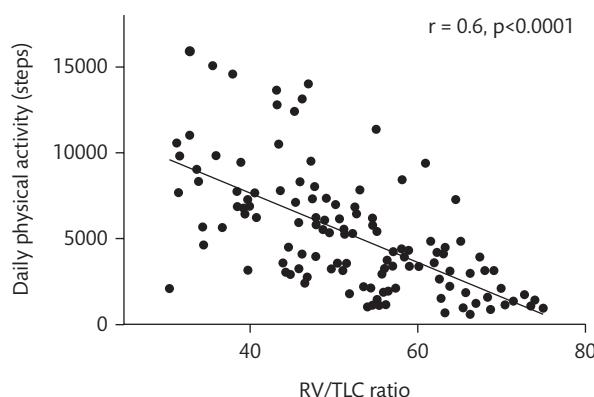


Fig. 18.8.21 Gas trapping, assessed as the proportion of residual volume to total lung capacity (RV/TLC), is inversely correlated with daily physical activity assessed as step counts measured using a triaxial activity monitor.

Figure courtesy of Dr Dinesh Shrikrishna.

- **Sputum production**—is this daily or only with exacerbations? What colour or volume? Is it difficult to clear? Has there been haemoptysis?
- **Impact of disease on patient's life**—including limitation of activities, economic impact, well-being, sexual activity, depression, and anxiety.
- **History of exacerbations and hospitalizations.** Have they ever required ventilatory support?
- **Multimorbidity**—the presence of multiple long-term conditions is the norm rather than the exception in COPD.
- **Heartburn**—gastro-oesophageal reflux is common in COPD and associated with greater exacerbation risk.
- **Weight loss**—may be a feature of COPD or comorbidity. Loss of appetite, difficulty swallowing, and breathlessness during meals may be present.
- **Social and family support**—social isolation is common in COPD patients. Are they in contact with patient support groups (e.g. in the United Kingdom, the British Lung Foundation runs 'Breathe Easy' groups)?
- **Nocturnal symptoms**—is there any evidence of sleep-disordered breathing? Breathlessness, paroxysmal nocturnal dyspnoea, orthopnoea, morning headaches. Prominent nocturnal symptoms may indicate another diagnosis such as asthma or cardiac failure.
- **Ankle swelling**—this may represent cor pulmonale or coexisting congestive cardiac failure.
- **Fatigue**—is a common but nonspecific symptom.
- **Exposure to risk factors**—smoking, occupational and environmental exposures, childhood history of chest disease or prematurity.
- **Family history**—of COPD or other chronic respiratory diseases.
- **Past history**—asthma, eczema, or hay fever suggesting a background of atopy. Allergies, respiratory infections in childhood, or prematurity.

And finally, and very importantly:

- **Likely prognosis**—if, after completing your assessment of a patient, you would not be surprised if they died in the next year, then this should prompt discussion about end-of-life care.

An overall clinical approach is described in Fig. 18.8.22.

Physical signs

In early COPD there may be few or no abnormal physical signs, with the diagnosis based on history and spirometry. Breathlessness may

Breathing SPACE – an approach for every breathless patient

- Smoking** – smoking cessation support for all
- Pulmonary disease** – offer prompt spirometry
 - prioritize high value care
- Anxiety** – identify and support psychosocial problems
- Cardiac disease** – dual diagnoses are common
 - don't undertreat
- Exercise** – pulmonary rehabilitation
 - encourage physical activity

Fig. 18.8.22 The breathing SPACE approach.

not be apparent at rest, but increased work of breathing with recruitment of accessory muscles occurs when walking and dressing/undressing. Some patients adopt a pattern of pursed lip breathing during expiration, which generates a positive expiratory pressure acting to splint airways open and delay lung emptying. A similar phenomenon at the laryngeal level can give rise to audible expiratory wheeze and transmitted upper airway sounds on auscultation of the chest.

Clubbing is not a feature of COPD, so if observed other causes such as chronic sepsis, pulmonary fibrosis, or malignancy should be considered. There may be nicotine staining due to smoking or a smell of smoke on clothes or hair. Forearm bruising is also common due to age-related loss of connective tissue supporting capillaries, exacerbated by the use of inhaled corticosteroids.

As COPD progresses and lung volumes increase patients may develop a hyperinflated, barrel-shaped chest, and an increase in the space in front of the trachea. Hoover's sign, an in-drawing of the lower ribs during inspiration as opposed to the normal expansion, is also characteristic of hyperinflation. Lung hyperinflation can lead to increased resonance on chest percussion with a loss of hepatic and cardiac dullness. The cardiac apex beat may be difficult to palpate and a more prominent liver edge, which should not be confused with hepatomegaly, may be palpable because the diaphragm is pushed down. The abdomen is often generally prominent for this reason.

Chest auscultation may be normal but will characteristically reveal quiet breath sounds with a prolonged expiratory phase. Wheeze may be present. A monophonic wheeze which does not clear with coughing should raise the possibility of a focal obstructive lesion such as a tumour.

Crepitations which do not clear with coughing are not typical of stable, uncomplicated COPD. They may represent acute lung infection, but if occurring in a stable patient they may represent an area of bronchiectasis or an additional or alternative diagnosis such as pulmonary oedema or pulmonary fibrosis.

A focused examination of the patient with COPD should look for evidence of pulmonary hypertension and cor pulmonale, including parasternal heave, a loud or split second heart sound, raised jugular venous pressure, and peripheral oedema. Tachycardia is common in COPD, as are atrial arrhythmias.

Central cyanosis may be apparent in patients who are hypoxic, particularly if there is accompanying polycythaemia. If hypercapnia is present there may be a bounding pulse and a coarse flapping tremor, known as asterixis.

Body mass index should be recorded as both over- and underweight are common in COPD. The latter increases the possibility of coexistent sleep-disordered breathing (see Chapter 18.5.2).

Clinical investigations

Pulse oximetry

This should be performed routinely in COPD patients to help classify disease severity and as a screening test to identify patients who may benefit from supplemental oxygen during exercise or at rest. Desaturation during exercise, particularly in patients with relatively mild airflow obstruction, may indicate the presence of pulmonary hypertension or pulmonary fibrosis. Measurement of arterial blood gases should be considered in patients with oxygen saturation 92%

or less and in patients with symptoms suggestive of sleep-disordered breathing.

Spirometry

Spirometry is the most important test for the definition of COPD, and also for evaluating the severity of lung function impairment (Fig. 18.8.23 and Table 18.8.2). It is important that this is carried out in a way that meets published standards such as those of the ATS/ERS. Spirometry is dependent on patient effort and coordination. The manoeuvre requires the individual to take a maximum breath in to total lung capacity and then breathe out as hard as they can to residual volume. Older bellows devices transcribed a trace onto paper; newer ones are electronic. The display should be large enough to see if the pattern of the trace is correct, does not stop abruptly, and is continuous without interruptions for breath or coughing. Spirometry should be performed seated. A good mouth fit is important and a nose clip is recommended. It is important to ensure that a full inspiration and maximum effort has been achieved. Three attempts should be made, and for reproducibility the FEV₁ should vary by less than 170 ml between manoeuvres.

To avoid the effect of airway collapse in patients with COPD during forced expiration, it is suggested that VC should be estimated by a slow or relaxed measurement, which allows patients to exhale at their own pace. The slow VC is often 0.5 litres greater than the FVC. This difference is itself an index of gas trapping. It is important that a volume plateau is reached when performing the FEV₁, which can take 15 s or more in patients with severe airways obstruction: if this manoeuvre is not carried out the FVC can be underestimated. The normal forced expiratory time is about 1 second per decade of age (i.e. roughly 5 seconds in a 50-year-old).

Spirometric measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race. The presence of a post-bronchodilator FEV₁/FVC ratio less than 0.70 confirms the presence of airflow limitation that is not fully reversible, which is an essential criterion for the diagnosis of COPD. As discussed earlier, there is debate about the use of a fixed ratio vs. the lower limit of normal. When considering a symptomatic individual in clinical practice, the fixed value is usually preferred. See Chapter 18.3.1 for further discussion.

Many electronic devices allow inspiration as well as expiration to be recorded to produce a flow volume loop (Fig. 18.8.24). In airflow obstruction the expiratory limb is concave upwards or 'scalloped'. The measurement of flow volume loops produces several other metrics that can be calculated to assess the degree of airflow obstruction. Expiratory flow rates at 75% or 50% of vital capacity

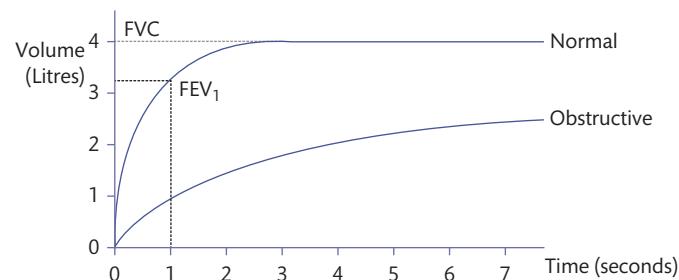


Fig. 18.8.23 Spirometry volume time curve in health and COPD.
Author's data.

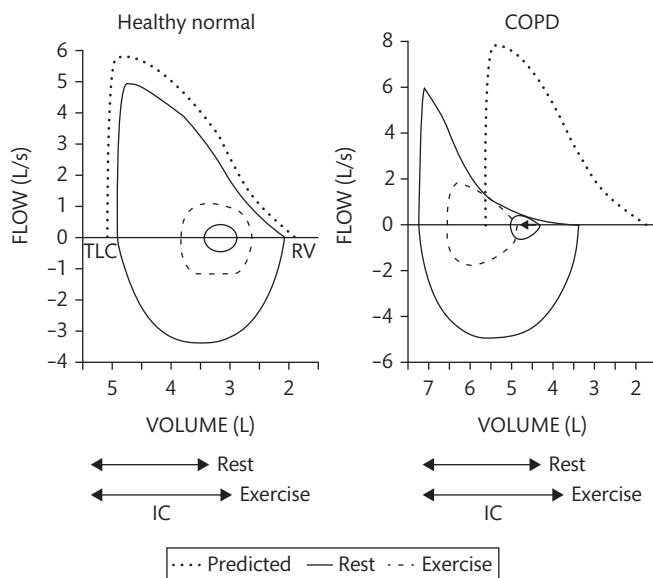


Fig. 18.8.24 Flow volume loops in health and COPD. The innermost trace is resting tidal breathing, the middle represents breathing during exercise and the outer the maximum flow volume loop.

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have been used as a measure of airflow limitation. These measurements are less reproducible than FEV₁, such that values must fall to below 50% of the predicted level to be regarded as abnormal. Flows at lung volumes less than 50% of vital capacity were previously considered to be an indicator of small airways function, but probably provide no more clinically useful information than measurements of FEV₁.

Peak flow rate is used to monitor lung function in asthma. The flow volume curves illustrate why peak flow rate may underestimate the physiological impairment in COPD. In COPD the peak flow rate achieved may be relatively preserved as the larger airways empty quickly, but there is then a rapid fall in flow rate due to dynamic airways collapse.

Reversibility testing

For classification of the severity of COPD, testing should be performed after the administration of bronchodilators to measure the extent of fixed airflow obstruction. As many patients are on long-acting bronchodilator medications anyway, this may simply translate into testing them on their usual medication. Reversibility testing is performed specifically to evaluate the response to treatment so differs from 'post-bronchodilator' testing. A large improvement in FEV₁ (>400 ml) may indicate the presence of asthma. This can be evaluated after acute administration of bronchodilation or after a trial of oral corticosteroids (e.g. 30 mg prednisone for two weeks). Reversibility testing is however a poor predictor of response to treatment. The ISOLDE study showed that there was no link between the response to two weeks of oral prednisone and subsequent response to inhaled corticosteroids. Likewise, bronchodilators may improve small airway function, reduce gas trapping, and thus reduce operating lung volumes and breathlessness without the FEV₁ changing significantly. This means that an absence of bronchodilator response does not necessarily mean that the treatment will

be ineffective and formal bronchodilator testing to guide treatment is no longer recommended.

Reversibility varies from day to day as different degrees of bronchial smooth muscle constriction can lead to different classification of reversibility status depending on the day of testing. Thus, when airway smooth muscle tone is higher, and thus FEV₁ is lower, a response to bronchodilators may be more likely to be achieved than when muscle tone is lower and FEV₁ is higher.

Gas transfer measurement

A low carbon monoxide transfer coefficient (K_{CO}) and transfer factor (TL_{CO}) are present in many patients with COPD and broadly reflect the degree of emphysema. The K_{CO} is the measured rate of uptake of CO, and the TL_{CO} is equal to this value multiplied by the alveolar volume (VA). The VA is measured by helium dilution. The process of gas trapping in emphysema means that the VA underestimates actual alveolar volume and in addition slow lung unit emptying means that the simple two compartment model that the calculation is based on is inaccurate. Accepting these limitations, TL_{CO} is the lung function parameter most strongly associated with survival in COPD and is also most closely associated with systemic effects, including loss of skeletal muscle bulk.

The commonly used method is the single-breath technique, which uses alveolar volume calculated from helium dilution during the single-breath test. It requires a vital capacity of 1.5 litres and the ability to breath-hold for 10 seconds. A steady state technique is also in use in some lung function labs.

Gas transfer is also reduced in pulmonary fibrosis and in pulmonary hypertension. These should be considered particularly in individuals with a disproportionately reduced gas transfer compared to the extent of airflow obstruction (e.g. an FEV₁ of 60% with a TL_{CO} of 30%). However, the possible combinations of airflow obstruction, ventilation inequality, and emphysema mean that a wide range of lung function patterns are possible without any additional diagnosis being necessary.

Lung volumes

The helium dilution technique used to assess alveolar volume for gas transfer measurements provides a measure of lung volumes including total lung capacity (TLC), residual volume (RV), and functional residual capacity (FRC). However, because of airway closure the helium does not mix with trapped gas and thus underestimates volume. Body plethysmography uses Boyle's law to calculate lung volumes from changes in mouth and sealed body box pressures. This does measure trapped air within the thorax, including poorly ventilated areas, and therefore gives higher readings for lung volumes than the helium dilution technique. Plethysmography is therefore preferred in COPD, especially where these measurements are used to guide treatment decisions such as eligibility for lung volume reduction procedures.

Arterial blood gases

Arterial blood gases are used to investigate possible hypoxaemia and hypercapnia in patients with COPD. This test is usually performed in stable patients with an FEV₁ less than 50% predicted or in those with clinical signs suggestive of respiratory failure or right heart failure. Respiratory failure is defined as a PaO₂ less than 8 kPa (60 mm Hg) while breathing air. This is referred to as Type 1 or

hypoxic respiratory failure if PaCO_2 is not elevated and Type 2 or hypercapnic respiratory failure if the PaCO_2 is more than 6.5 kPa (50 mm Hg).

It is essential that the inspired oxygen concentration is specified when reporting blood gas results. It may take at least 30 min to reach a steady state after the inspired oxygen concentration is changed because of long time constants for alveolar gas equilibration in COPD.

Acid-base status can also be assessed from the arterial pH (hydrogen ion concentration) and the bicarbonate. Increases in Paco_2 , which can occur rapidly, can be compensated by renal conservation of bicarbonate ions, which is a relatively slow process. Acid-base status, particularly mixed respiratory and metabolic disturbances, can be characterized by plotting values on an acid-base diagram (Fig. 18.8.25).

Exercise tests

Impairment of functional exercise capacity is a key feature of COPD and can be evaluated in several ways.

The purposes of testing may include diagnosis, evaluation of maximum capacity, assessment of response to an intervention, and identification of specific physiological responses (e.g. desaturation, tachycardia).

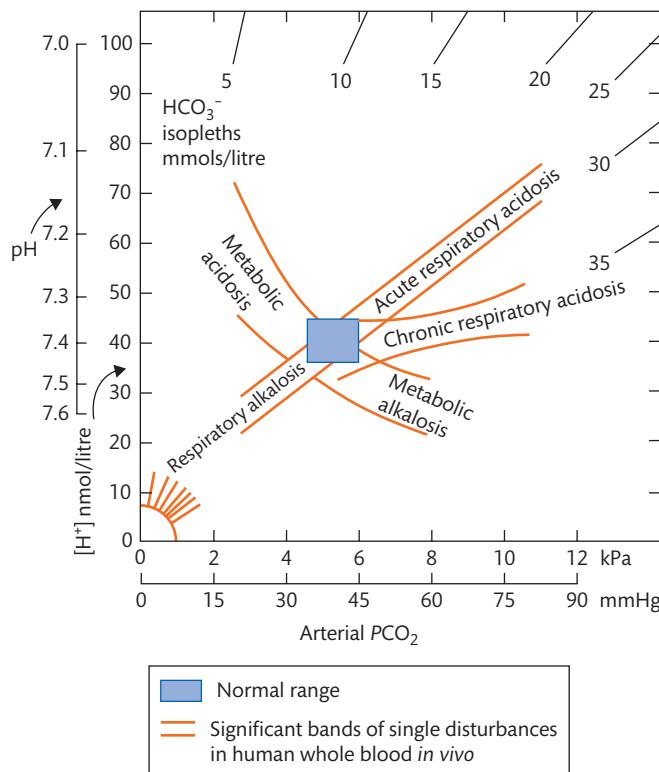


Fig. 18.8.25 A nonlogarithmic acid-base diagram derived from the measured acid-base status of patients within the five abnormal bands illustrated and of normal subjects (hatched box). This plot of CO_2 tension against hydrogen ion concentration (pH) allows the likely acid-base disturbance and calculated bicarbonate value (obtained from the relevant isopleth) to be rapidly determined, while changes during treatment can be plotted serially for each patient.

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Laboratory-based cardiopulmonary exercise testing is usually carried out on either a treadmill or cycle ergometer. The latter may be preferred in COPD as it provides a more stable platform and patients can use their arms to stabilize their upper ribcage. However, for most people walking on a treadmill is more relevant to daily activities than cycling. Symptom limited exercise tests are usually stopped because of breathlessness or leg fatigue. The test used may alter the locus of limiting symptoms; a higher proportion of COPD patients will stop cycling because of leg fatigue than report this as a factor limiting them when they walk.

Exercise tests may be incremental to assess maximum capacity, or endurance to evaluate performance at a percentage of maximum capacity. Because of the power-time relationship, endurance tests may be more responsive to interventions than incremental ones.

In laboratory tests, a metabolic cart with a mask or mouthpiece used to measure ventilation and analyse expired gas allows calculation of oxygen consumption and CO_2 production. Although considered the 'gold standard', this form of testing requires expensive equipment and a high level of training to ensure accurate results. For many purposes, simpler field tests are as useful and therefore represent better value.

The six-minute walking test requires the subject to walk as far as they can for 6 minutes. It requires a course of at least 30 m and is the most widely used field walking test. Outcomes include distance walked, limiting symptoms and heart rate, and oxygen saturation can also be measured. The ATS has produced guidance on its correct implementation.

The Incremental Shuttle Walking Test (ISWT) involves walking between two cones 10 m apart before a beep sounds. As the interval between beeps shortens, the person has to walk more quickly. The test stops when they are unable to keep up with the pace. A practice walk is done first and the better of the two results taken. An endurance shuttle walk test is performed in the same course but at a fixed speed (interval between beeps) set to correspond to 85% of the peak walking speed on an ISWT. The main outcome of this is the endurance time.

Walking tests are reproducible and responsive to change, but need to be performed correctly, in particular the use of practice walks. Values are associated with breathlessness, health status, and survival and are included in some prognostic indices such as the BODE score.

α_1 -antitrypsin

α_1 -Antitrypsin is a polymorphic glycoprotein that is a potent inhibitor of serine proteases, with greatest affinity for the enzyme neutrophil elastase. It is synthesized in the liver and increases from its usual plasma concentration of about 2 g/litre as part of the acute phase response. Reduced A1AT activity increases lung damage occurring in response to cigarette smoke and is associated with accelerated lung function decline.

α_1 -Antitrypsin levels and phenotype should be measured in all patients who present with COPD at a young age (<50 years), and in those with a family history of COPD at an early age. A serum concentration of 15–20% of the normal value is highly suggestive of homozygous α_1 -antitrypsin deficiency. Some guidelines recommend α_1 -antitrypsin assessment for all patients with COPD to improve case finding in relatives. See Chapter 12.13 for further discussion of α_1 -antitrypsin deficiency.

Other routine tests

Routine electrocardiography can be useful in the assessment of patients with COPD though it is an insensitive technique in the diagnosis of cor pulmonale. However, an argument can be made in its favour given that comorbidities are common, including rhythm disturbances, and some medications can prolong the QT interval.

A full blood count may reveal anaemia of chronic disease, which commonly occurs in COPD. Polycythaemia may be present in patients with severe COPD and predisposes to vascular events. It should be suspected when the haematocrit is greater than 47% in women and 52% in men, and/or the haemoglobin is greater than 16 g/dl in women and 18 g/dl in men, provided other causes of spurious polycythaemia, due to decreased plasma volume, such as caused by dehydration or diuretics, can be excluded.

Imaging

Chest radiography

The most basic imaging modality is chest radiography. It is usually normal in early disease and may be so in individuals with significant impairment. As COPD progresses the lung fields may become hyperinflated, with flattening of the diaphragms such that the border of the diaphragm in the midclavicular line is at or below the anterior end of the sixth rib (Fig. 18.8.26). The accuracy of chest X-ray in COPD is low, but it may be useful for excluding alternative diagnoses and identifying co-occurring conditions such as fibrosis,

bronchiectasis, and cardiac failure. Routine repeat chest X-rays are not indicated in the follow-up of patients with COPD.

Chest radiology appearances of lung hyperinflation include:

- a low flattened diaphragm;
- increased retrosternal air space occurs when the horizontal distance from the anterior surface of the aorta to the sternum exceeds 4.5 cm on the lateral film at a point 3 cm below the manubrium;
- an obtuse costophrenic angle on the posterior–anterior or lateral chest radiograph;
- inferior margin of the retrosternal air space is 3 cm or less from the anterior aspect of the diaphragm.

The vascular changes associated with emphysema result from loss of alveolar walls and appear as:

- a reduction in size and number of pulmonary vessels, particularly at the periphery of the lung;
- vessel distortion, producing increased branching angles, excess straightening, or bowing of vessels;
- areas of increased lucency;
- hilar vessels may be prominent.

A general increased transradiancy may be due to the chest radiograph being overexposed. Focal areas of transradiancy surrounded by hairline walls represent bullae (Fig. 18.8.27). These may be multiple, as part of a generalized emphysematous process, or localized. An ‘increase in lung markings’ rather than areas of increased transradiancy has often been described in patients with COPD: the cause of these changes is unknown, but may at least be contributed to by nonvascular linear opacities due to scarring.



Fig. 18.8.26 Chest radiograph shows hyperinflated lung fields with flattening of the diaphragm.



Fig. 18.8.27 Chest radiograph shows bullous changes, particularly marked in the upper zones.

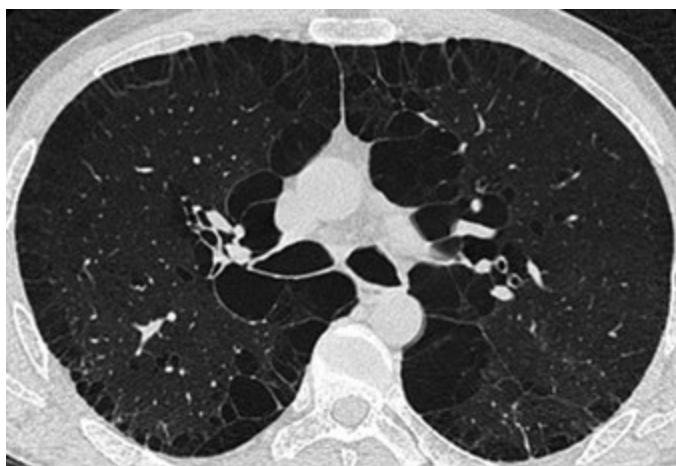


Fig. 18.8.28 Well-demarcated peripheral emphysema on thoracic CT scan.

Thoracic CT scanning

CT scanning is increasingly used for the evaluation of COPD (Fig. 18.8.28 and 18.8.29). It can provide information about

- the extent of emphysema;
- the type of emphysema (centrilobular vs. panacinar);
- the pattern of emphysema—especially homogenous vs. heterogeneous;
- integrity and position of interlobar fissures;
- airway disease—airway wall thickening, bronchiectasis;
- vascular abnormalities—increase in pulmonary artery/aorta ratio;
- presence of other lung conditions—pulmonary fibrosis, pleural plaques, lung nodules, and masses.



Fig. 18.8.29 'Moth-eaten appearance' of centrilobular emphysema on thoracic CT scan.

CT scans are usually interpreted based on visual appearances, but quantitative techniques have been developed. At present these are mostly in use for research purposes only. Microscopic emphysema can be quantified by measuring CT lung density, which is expressed on a linear scale in Hounsfield units (water = 0; air = -1000). Density masking techniques quantify the area of lung with a density below a certain threshold of Hounsfield units (e.g. -950 or -910 HU) which is taken to represent emphysema. Emphysema scored in this way is associated with lung function, symptoms, and mortality risk. One limitation is that lung density depends on lung volume so there are technical concerns evaluating change over time as TLC increases with worsening disease. A related approach is to calculate the fifteenth percentile mean lung density, the PD15. This measure has been shown to be responsive to change in clinical trials.

Emphysema occurs in three main histological patterns; centrilobular/centriacinar, paraseptal, and panacinar. In centrilobular emphysema CT shows low attenuation areas with ill-defined margins producing a 'moth-eaten' appearance. It tends to occur more in the upper zone, particularly in early disease. Panacinar emphysema produces a more uniform appearance of low attenuation lung and occurs more frequently in the lower parts of the lung. These two patterns frequently occur in the same individual. Paraseptal emphysema occurs adjacent to connective tissue structures with appearances that highlight interlobular septa so that emphysematous areas, which are usually peripheral, are highly demarcated. The typical pattern of disease in α_1 -antitrypsin deficiency is lower lobe predominant, pan-acinar emphysema with airway wall thinning, but any COPD phenotype can occur.

CT scanning is crucial for identifying patients with the appropriate pattern of emphysema for lung volume reduction procedures and should be considered in patients with an FEV₁ below 50% and if there is concern about pulmonary fibrosis or bronchiectasis. CT can be helpful in distinguishing airways predominant phenotypes from emphysematous pattern. Airways abnormalities include bronchial wall thickening, areas of focal air trapping (mosaicism) and mucus plugging.

CT scans in patients with COPD frequently reveal nodules, 95% of which are not malignant but they may require follow-up (the British Thoracic Society has recently produced guidance). The use of CT to screen high risk populations for lung cancer is relevant to patients with COPD, the presence of which is itself a risk factor for lung malignancy, independent of smoking. CT screening may identify emphysema in individuals without a prior diagnosis of COPD. Other infiltrative processes including respiratory bronchiolitis interstitial lung disease (RB-ILD), Langerhans cell histiocytosis and interstitial fibrosis may also be identified.

Pulmonary vascular changes can also occur in COPD. In health, the aorta has a greater diameter than the pulmonary artery. Increase in pulmonary artery dimensions and thus in the PA/A ratio may indicate the presence of pulmonary hypertension. Data from the COPDGene and ECLIPSE cohorts has shown that a PA/A ratio more than 1 is associated with greater exacerbation risk.

The presence of coronary artery calcification is a frequent incidental finding which may have prognostic implications and be an indication for further investigation. Evidence of osteoporosis is also common.

Table 18.8.9 Composite prognostic indexes in chronic obstructive pulmonary disease

Composite Index	Components
BODE	BMI, FEV ₁ , mMRC, 6MWD
i-BODE	BMI, FEV ₁ , mMRC, ISWT
mBODE	BMI, FEV ₁ , mMRC, peak $\dot{V}O_2$
eBODE	BMI, FEV ₁ , mMRC, 6MWD, exacerbation rate
BODEx	BMI, FEV ₁ , mMRC, exacerbation rate
Inflammatory BODE	BODE, inflammatory biomarkers, age, and hospitalization history
ADO	Age, mMRC, FEV ₁
DOSE	mMRC, FEV ₁ , smoking status, exacerbation rate
CODEx	Comorbidity, obstruction, dyspnoea, and previous severe exacerbations

Definition of abbreviations: 6MWD, 6-minute-walk distance; ADO, age, dyspnoea, and airflow obstruction index; BMI, body mass index (kg/m^2); BODE, body mass index, airflow obstruction, dyspnoea, and exercise capacity index; BODEx, exacerbations replace 6MWD in the original BODE; CODEx, comorbidities, airflow obstruction, dyspnoea, and exacerbations index; DOSE, dyspnoea, airflow obstruction, smoking status, and exacerbations index; eBODE, exacerbations added to original BODE; FEV₁, forced expiratory volume in 1 second (severity of airflow obstruction); inflammatory BODE, inflammatory markers added to original BODE; mBODE, modified BODE in which 6MWD is replaced by peak oxygen consumption; mMRC, level of dyspnoea according to the Modified Medical Research Council questionnaire.

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Contrast-enhanced CT is usually not indicated unless there is specific concern about the possibility of thromboembolic disease.

Echocardiography

This can be useful in COPD, though lung hyperinflation may make it more technically challenging because aerated lung reduces the acoustic window. It allows assessment of pulmonary arterial pressure as well as identification of right heart strain including right-sided chamber dilatation. As cardiac comorbidities are common, incidental left-sided and valvular disease may also be identified in patients with COPD.

Combined COPD scoring systems

Although FEV₁ provides a simple measure of airflow limitation, this only captures one element of the impact of COPD on lung function, and it is well recognized that lung function is only one element of this complex disease. For these reasons, a range of scoring systems have been proposed, which capture other features including measures of breathlessness, exercise capacity, exacerbation frequency, body mass index, and health-related quality of life, as well as age (Table 18.8.9). These can be used to stratify patients for treatment and to estimate prognosis.

BODE index

For prognosis, the most widely used score is the BODE index which includes body mass index, airflow obstruction (FEV₁),

Table 18.8.10 The body mass index, airflow obstruction, dyspnoea, and exercise capacity (BODE) index in COPD

Variable	Points on BODE index			
	0	1	2	3
FEV ₁ (% predicted)	≥65	50–64	36–49	≤35
Distance (m) walked in 6 min	≥350	250–349	150–249	≤149
MRC dyspnoea scale	0–1	2	3	4
Body mass index	≥21	≤21		

dyspnoea (mMRC score), and exercise capacity (Table 18.8.10). The hazard ratio for death from any cause increases by 1.34 and for respiratory death by 1.62 for every point increase on the BODE scale. It should be noted, however, that although the estimates are useful at a population level they are of limited accuracy for individual patients. A modified version of this, the i-BODE, uses a different walking test, substituting the ISWT for the 6MWT.

GOLD classification

The 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD—<https://www.goldcopd.org>) COPD classification system incorporated only FEV₁ and hypoxia:

- Stage I:** Mild FEV₁ ≥80% predicted
- Stage II:** Moderate 50% ≤FEV₁ <80% predicted
- Stage III:** Severe 30% ≤FEV₁ <50% predicted
- Stage IV:** Very severe FEV₁ <30% predicted or FEV₁ <50% predicted plus chronic respiratory failure

This has developed such that the 2017 GOLD classification now combines the extent of airflow obstruction (stage I to IV) with a category based on symptom burden and exacerbation history (A–D) (Fig. 18.8.30). To use this classification assessment first identify the extent of airflow obstruction, then assess symptoms with the mMRC dyspnoea score or the CAT score—less symptomatic (left boxes mMRC 0–1, CAT <10) or more symptomatic (right boxes mMRC ≥2 or CAT ≥10). Next, assess the risk of exacerbations using the GOLD spirometric grade (GOLD 1–2 low risk lower boxes, GOLD 3–4 high risk upper boxes), or assess the number of exacerbations the patient has had in the last 12 months (0–1 low risk, lower boxes, 2 or more high risk upper boxes). If the latter case the method giving the highest risk should be chosen. This form of assessment categorizes patients into four symptom groups and four airflow categories:

Patient group A—Low risk, less symptoms

Patient group B—Low risk, more symptoms

FEV1 (% predicted)		Assessment of symptoms/risk of exacerbations		
GOLD I	>80			
GOLD II	50–79	≥2 exacerbations (or ≥1 requiring hospital admission)	C	D
GOLD III	30–49	0 or 1 exacerbations (not leading to hospital admission)	A	B
GOLD IV	<30		Symptoms mMRC 0–1 mMRC ≥2 CAT <10 CAT ≥10	

Fig. 18.8.30 GOLD 2017 COPD classification—association between symptoms, spirometric classification, and risk of exacerbations in COPD—see text for discussion.

Patient group C—High risk, less symptoms

Patient group D—High risk, more symptoms

This classification should have the advantage of encouraging a holistic approach to COPD evaluation, incorporating information systematically that can be used to guide treatment. A disadvantage is that the boundaries between categories are arbitrary and may change over time, adding complexity. The ‘holistic’ nature of the score may even be a problem, as more symptomatic individuals (Grade B) may be symptomatic for reasons other than COPD (e.g. obesity or comorbidities such as cardiac disease or anxiety).

Differential diagnosis

COPD needs to be distinguished from other causes of breathlessness (Table 18.8.11). The features noted in Table 18.8.11 tend to be characteristic of the respective diseases, but do not occur in every case. Furthermore, there could be overlap between two or more categories, and diseases might coexist.

Although the differences between asthma and COPD have historically been emphasized, both diagnostic categories encompass a range of phenotypes and both are common conditions. The diagnosis of asthma itself predicts COPD in later life, and it can be impossible to make a precise distinction between the two clinically, particularly where there is a significant smoking history. Bronchiectasis can occur in the absence of airflow obstruction, but the pathological features of airway wall thickening and airway dilatation are frequently present in patients with COPD, meaning that it also occurs as a COPD phenotype rather than a distinct condition. TB is strongly associated with smoking and there is an association between TB and increased risk of COPD. Congestive cardiac failure is a common comorbidity of COPD. Connective tissue disease should be considered as well as conditions that sometimes mimic COPD (e.g. lymphangioleiomyomatosis and histiocytosis X).

Table 18.8.11 Differential diagnosis of COPD

Diagnosis	Suggestive features
COPD	Onset in midlife Slowly progressive symptoms Smoking history
Asthma	Symptoms since childhood Variable symptoms—day to day and at night History of atopy Nasal symptoms
Congestive heart failure	Basal crepitations on chest auscultation Cardiomegaly on chest radiograph ECG abnormalities Restrictive spirometry History of hypertension or ischaemic heart disease
Bronchiectasis	Large volumes of purulent sputum Episode of severe chest disease in childhood Radiograph shows bronchial dilatation or wall thickening
Interstitial lung disease	Fine end-inspiratory crepitations Restrictive spirometry Desaturation on exercise Connective tissue disease Medications (e.g. amiodarone, nitrofurantoin)
Tuberculosis	Classic radiographic findings Fever, night sweats High local prevalence Microbiological confirmation
Obliterative bronchiolitis	Onset in young age and nonsmokers History of fume exposure or rheumatoid arthritis CT scan shows hypodense areas on expiration
Diffuse panbronchiolitis	Patients typically male nonsmokers History of chronic sinusitis CT scan shows diffuse centrilobular nodular opacities and hyperinflation

Management of stable COPD

Although the underlying pathophysiology of COPD is largely irreversible, optimum management of COPD can improve symptoms and exercise capacity, reduce exacerbations, and in some instances

Table 18.8.12 Goals of COPD management

Reduce decline in lung function
Improve day to day symptoms
Minimize side effects of treatment
Prevent exacerbations
Improve survival
Address physical and mental health/comorbidities
Manage resources—value, sustainability, and distributive justice
Promote patient autonomy and appropriate self-management
Provide good quality end-of-life care

improve survival. The goals of COPD management are shown in **Table 18.8.12** and **Fig. 18.8.31**.

There are many national guidelines for COPD. In the United Kingdom a National Institute for Clinical Excellence (NICE) guideline is available, together with a Quality Standard Document for service delivery published in 2011, as well as a range of subsequent updates on therapies (see <http://www.nice.org.uk/guidance/conditions-and-diseases/respiratory-conditions/chronic-obstructive-pulmonary-disease>). Joint guidelines on COPD, from the ATS, ERS, ACP, and ACCP were published in 2011. Subsequent joint statements on integrated care for COPD patients, on pulmonary rehabilitation, on the use of field walking tests, and identifying outstanding research questions have also been published (see <http://www.thoracic.org/statements/copd.php>). The GOLD project also produces international guidelines for COPD management (see <http://www.goldcopd.com/>).

Management priorities in COPD should be those interventions which are the best value. The London Respiratory Network, working

with the London School of Economics, has produced a 'Pyramid of Value' graphic to focus attention on these (**Fig. 18.8.32**).

Vaccination

Annual influenza vaccination is recommended as it has been shown to reduce exacerbations and mortality from influenza in patients with COPD. The vaccine is adjusted each year to improve effectiveness against circulating strains.

Pneumococcal vaccination is intended to reduce the risk and severity of streptococcal pneumonia, the commonest cause of community-acquired pneumonia. It is recommended for patients with COPD aged 65 years and older, as well as those under 65 years of age with FEV₁ less than 40% predicted, in whom it has been shown to reduce the incidence of community-acquired pneumonia.

Smoking cessation

Smoking cessation is crucial to prevent COPD and also a crucial part of the management of the condition. Smoking cessation improves survival in COPD patients (**Fig. 18.8.33**) and also reduces symptoms, in particular cough and sputum production. A Making Every Contact Count approach should be adopted so that every health professional is trained and motivated to give very brief smoking cessation advice on each occasion that they encounter the patient (**Table 18.8.13**). Online training is available in the United Kingdom from The National Centre for Smoking Cessation and Training. Acute exacerbations are opportunities to intervene and times when patients may be especially motivated to quit.

Because smoking cessation produces such dramatic health benefits, the value of interventions rises the more intensive and effective they are (**Table 18.8.14**).

Around 80% of smokers start before they are 20, so smokers with COPD will have a long history of smoking and may well have

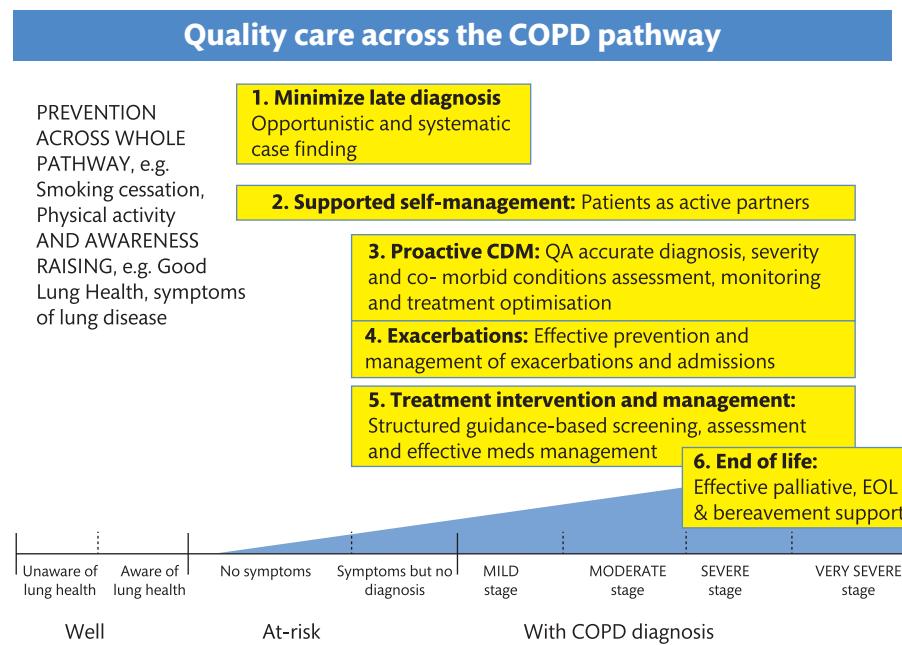


Fig. 18.8.31 Quality care across the COPD pathway. CDM, chronic disease management; QA, quality assured; EOL, end of life.

From 'An Outcomes Strategy for COPD and Asthma in England', Department of Health, © Crown copyright 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216139/dh_128428.pdf

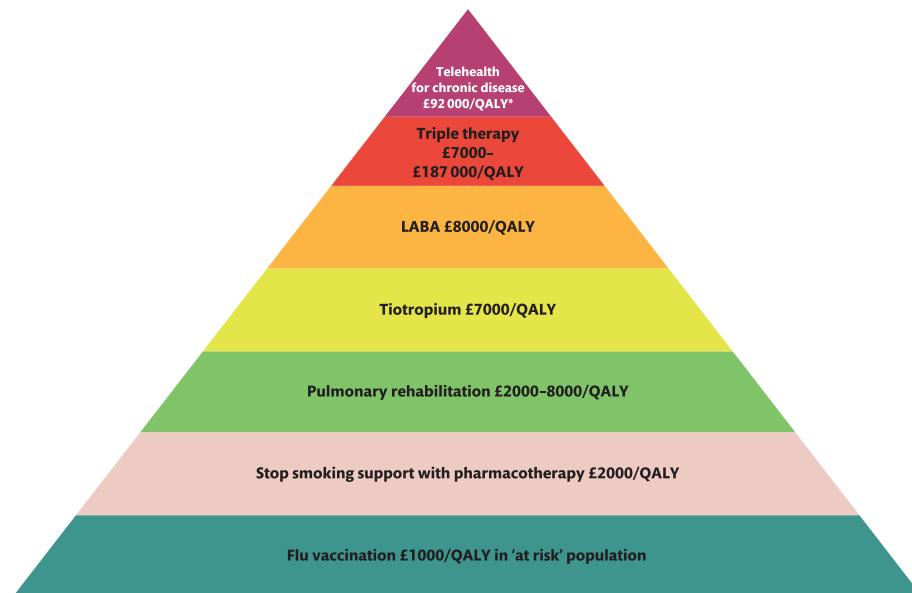


Fig. 18.8.32 Pyramid of value for COPD interventions. Relative value expressed as cost per quality-adjusted life year (QALY) if different COPD interventions.

Developed by the London Respiratory Network and the London School of Economics.

made quit attempts previously. Advice to quit smoking should be objective and nonjudgemental. Many smokers with COPD express guilt at continuing to smoke and may avoid discussion of the subject. It may be helpful to highlight that their addiction often started in childhood. In addition, considerable scientific effort by the tobacco industry has gone into making tobacco products as addictive as possible. This includes manipulating the pH to increase the solubility of nicotine and masking this with flavourings such as menthol to produce a 'smooth' taste.

Counselling should include an assessment of the level of addiction (the Fagerstrom index) and motivational interviewing to promote desire to quit. Reasons why quitting would be of benefit to them should be outlined, but also the factors that motivate them to continue smoking should be explored. Counselling can be effective in

Table 18.8.13 Very brief smoking cessation advice

ASK	Assess current and past smoking behaviour
ADVISE	Provide information on consequences of smoking and smoking cessation. Advise person quit smoking
ASSIST	Provide options for later/additional support Advise on stop smoking medications

both individual and group sessions, depending on personal preference and resources.

Increasing exercise levels is often recommended, though the evidence that it actually promotes smoking cessation itself is weak.

Smoking cessation is associated with withdrawal symptoms including mood disturbance, anxiety, increased appetite, vivid dreams, and gastrointestinal disturbance. Anxiety and stress are often given as reasons to delay or defer quit attempts, and as reasons for relapse. Smokers should be reassured that nonsmokers and ex-smokers actually experience less anxiety symptoms than smokers. Smoking cessation in COPD patients has been associated with weight gain, but this includes an increase in lean body mass and therefore may be beneficial.

Nicotine replacement therapy

Nicotine replacement therapy (NRT) can be delivered in several ways, including patches, gum, inhalators, nasal spray, and lozenges. The optimum approach includes a slow release background

Table 18.8.14 Value of smoking cessation interventions in COPD

	1 year abstinence rate	Cost per QALY
Usual care	1.4%	
Minimal counselling	2.6%	£14 735
Intensive counselling	6%	£7149
Intensive counselling + pharmacotherapy	12.3%	£2092

Data from Hoogendoorn M, et al. (2010). Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. *Thorax*, 65, 711-8.

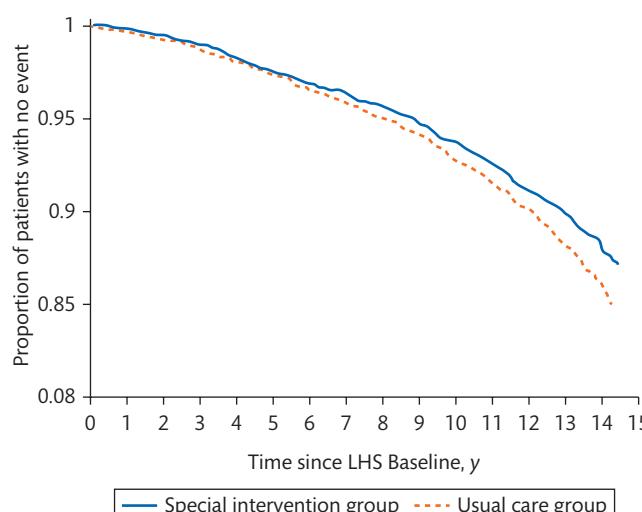


Fig. 18.8.33 Smoking cessation improves survival in COPD.

Reproduced from Anthonisen NR, et al. (2005). The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*, 142(4), 233-9, Copyright © 2005, The American College of Physicians.

delivery mechanism such as a patch, combined with a more rapid onset system such as gum or spray which can be used acutely when cravings occur. Some patches work for 24 hours and some 16 hours, the latter being intended to cover waking hours only.

Nicotine delivered in this way has few harmful effects and can always be considered less harmful than smoking, but NRT should be avoided during acute coronary syndromes because of vasoconstricting effects. There have also been concerns that nicotine should also be avoided in pregnancy because it was thought to be associated with low birth weight, but NRT is much less harmful than smoking to mother and fetus, and the SNAP trial in pregnant smokers has demonstrated that NRT was associated with better long-term child outcomes.

E Cigarettes

Many smokers find that they are able to satisfy their nicotine addiction by using e-cigarettes. These devices heat a liquid carrying agent (propylene glycol or vegetable glycerin) which contains varying concentrations of nicotine as well as a range of flavours. Inhaling vapour is substantially safer than smoking, so as long as smokers switch completely to vaping they are likely to substantially reduce their risk of harm, and doing so has been reported to produce improvements in COPD exacerbation rates, COPD assessment tool scores, and 6-minute walking distance over a 3-year period. Some toxicity has been identified, so people with COPD who have quit smoking this way should be advised to try to quit vaping too if they can, though not at the expense of going back to smoking.

Varenicline

This medication is a partial agonist of the nicotine receptor, reducing cravings but also blocking the acute effect of smoking and thus breaking the cycle of reinforcement. It is the most effective pharmacological approach, and usually used for 12 weeks, with a 2 week run in period

before the quit date, while the dose is uptitrated. Gastrointestinal side effects are common. Mood disturbances can occur, which improve when the medication is stopped. Large population studies have shown that early concerns that it may be associated with increased suicide risk are not justified, and the EAGLES trial showed that it can be given safely in people with mental health problems.

Bupropion

This tricyclic antidepressant is also licenced for smoking cessation. It is contraindicated in patients with a history of epilepsy.

Repeat quit attempts

The best time to attempt to quit smoking is when a person has just relapsed, before they have fully re-established their smoking habit. Strategies that ration supported quit attempts may therefore be counter-productive. Similarly, time limits to the duration of treatment support should not be too strict. More prolonged treatment may be appropriate in heavily addicted individuals who are at an increased risk of relapse.

Pulmonary rehabilitation

Pulmonary rehabilitation is a supervised programme of exercise training combined with education to help patients to understand their condition and self-manage. The 2015 Cochrane Review of Pulmonary Rehabilitation confirmed the strong evidence base for the therapy, which is one of the highest value interventions in COPD. It improves exercise capacity (Fig. 18.8.34), breathlessness, and health status as well as anxiety. It is also associated with reduced hospital admissions. These improvements exceed the minimum clinically important difference and generally exceed the benefits seen with pharmacotherapy. It is important that clinicians are aware of this, so they can confidently explain the concept to patients who may be wary of exercise after a long period of avoiding exertion because of the symptoms it provokes. In addition, observational

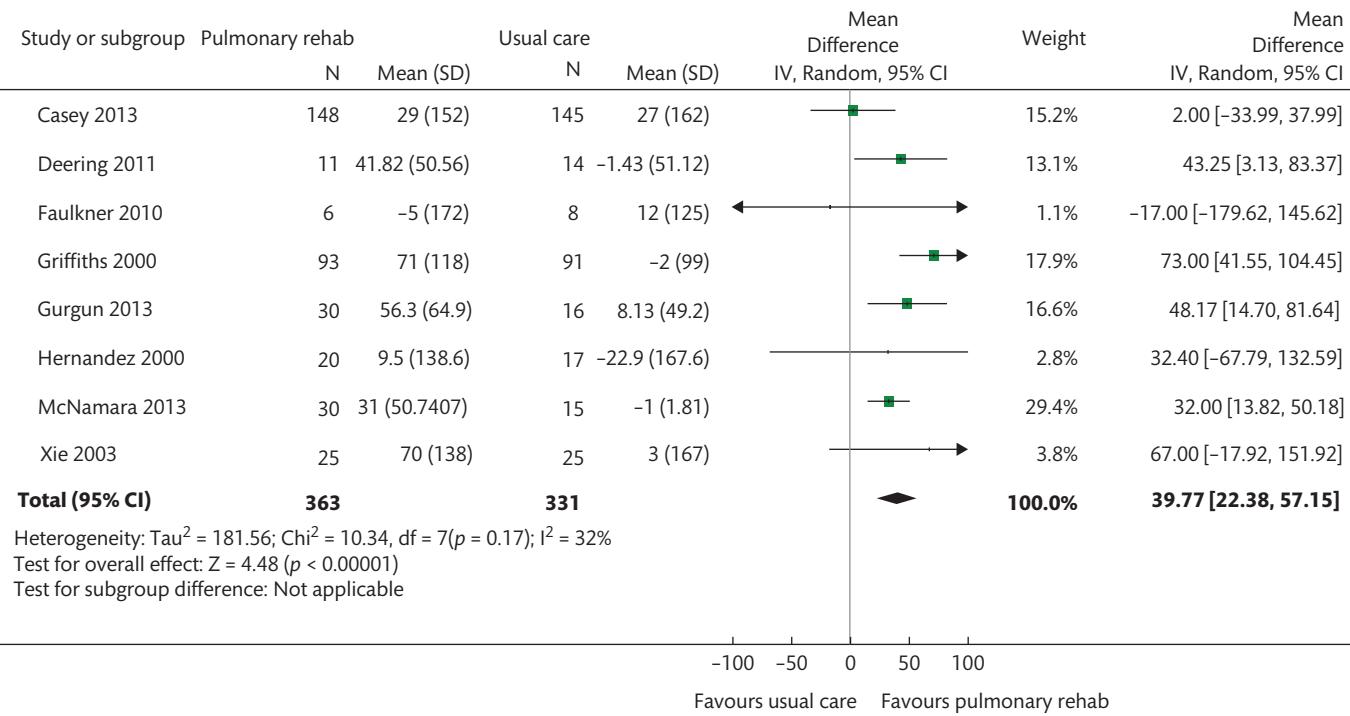


Fig. 18.8.34 This Cochrane review highlights the effectiveness of pulmonary rehabilitation in COPD.

From McCarthy B, et al. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015, Issue 2, CD003793.

data suggest that pulmonary rehabilitation works ‘in the real world’. The benefits seen in patients who complete clinical programmes are of a similar magnitude to those seen in randomized clinical trials.

Although the evidence base for pulmonary rehabilitation is extremely strong, there are many outstanding questions regarding the optimum duration of programmes, location, and training modalities, as well as whether and how often programmes should be repeated. A typical programme includes a mixture of aerobic and strength training. The former may involve free walking, treadmills, or exercise bikes, and other specialized equipment. Fixed gym equipment, free weights, or elastic resistance bands are often used for strength training. Exercise prescription is based on an initial assessment, usually a walking test, although some programmes use more complicated cardiopulmonary exercise testing.

Programmes typically last a minimum of six weeks and usually consist of twice weekly sessions with additional home exercise. As the programme progresses the level of exercise should be increased. It is crucial that patients are encouraged to develop a home exercise regime during the course so that they can continue to exercise once the programme is finished. Behaviour change is an important goal, but this may require longer than is necessary to achieve initial benefits in walking distance and other measures. Continuation exercise programmes, sometimes organized by groups of patients and in some situations available on prescription, can be helpful, but must not be considered a substitute for a properly constituted pulmonary rehabilitation programme itself.

It is clear that a true training effect, with lower lactate production for a given workload, can be achieved in COPD. In addition to this effect, there is also a psychological effect, with pulmonary rehabilitation operating as a graded exposure therapy, in effect addressing ‘phobia’ about exercise and breathlessness.

A minimum outcome set, both to assess individuals and to evaluate the effectiveness of the programme itself, should include a walking test (e.g. ISWT, 6MWD), and a health status measure (e.g. CAT score or CRDQ or CCQ). The HAD score, which generally improves following pulmonary rehabilitation, is used as a screening tool to identify patients who may benefit from additional psychology input or referral. The Lung Information Needs Questionnaire (LINQ) can be used to assess the impact of education programmes.

All patients with significant breathlessness (MRC dyspnoea score ≥ 3) should be considered for pulmonary rehabilitation, as should those who consider themselves to be limited. The cut off for treatment is arbitrary and based partly on resources: patients with less breathlessness do benefit from pulmonary rehabilitation and should also be encouraged to exercise, but they may well be able to do this in a more conventional environment.

The educational programme for pulmonary rehabilitation should cover a range of topics, and programmes should be staffed by a range of health professionals including physiotherapists, occupational therapists, health psychologists, nurses, pharmacists, and smoking cessation advisors (**Table 18.8.15**).

Pulmonary rehabilitation is a group activity and may also serve to reduce the social isolation experienced by many older people with severe lung disease that limits their mobility. It is also a holistic therapy with potential benefits to comorbidities that COPD patients have as well as COPD itself.

Inspiratory muscle training is sometimes incorporated into pulmonary rehabilitation programmes. Although it is possible to improve performance on tests of inspiratory pressures with practice, it is not clear that these improvements actually translate into

Table 18.8.15 Topics to cover in pulmonary rehabilitation

Breathing strategies	Early treatment
Proper use of medications	When and how to contact healthcare providers
Smoking cessation	Eating properly
Exercise	Travel/sex/leisure
Dealing with anxiety/panic attacks	Lung function
Move from teaching to self-management	

clinical benefit. The National Emphysema Therapy Trial (NETT) study demonstrated that maximum inspiratory pressures improve after pulmonary rehabilitation in the absence of specific inspiratory muscle training, and routine use cannot be recommended.

Post-exacerbation pulmonary rehabilitation

Several trials have addressed the specific issue of post-exacerbation pulmonary rehabilitation, with patients enrolled in a program within 2 weeks of discharge from hospital. It is a highly effective intervention in this context. A 2011 Cochrane review found that it significantly reduced hospital admissions (pooled odds ratio 0.22 [95% CI 0.08–0.58], number needed to treat (NNT) 4 [95% CI 3–8], over 25 weeks), and mortality (OR 0.28; 95% CI 0.10–0.84), NNT 6 [95% CI 5–30] over 107 weeks).

Pharmacotherapy

Inhaled therapies form the basis of pharmacological treatment for COPD. They have two broad functions: bronchodilatation and suppression of the inflammatory response. There are two classes of bronchodilator: anticholinergic drugs and β_2 -agonists. These are available in short-acting as required forms, and long-acting (once or twice daily treatment) forms. Inhaled corticosteroids are beneficial in some patient groups, but inflammation in COPD typically displays only limited corticosteroid sensitivity. Inhalers which include a combination of long-acting bronchodilators and corticosteroids are frequently used.

Other medications include theophyllines and mucolytics. Long-term antibiotic therapy may have a role. With the advent of non-invasive ventilation, respiratory stimulants are rarely used.

Clinical trials in COPD have generally studied the effects of medications in largely undifferentiated COPD populations. This means that modest overall effects may disguise greater (or lesser) effects in specific patient phenotypes. Studies have also in general excluded patients with significant comorbidity, which has implications for the general applicability of findings in clinical practice.

Inhaler technique

Existing inhaler devices are relatively inefficient, with only a small proportion of drug delivered to the target region. This depends on factors including means of activation, particle size, and patient compliance with the required inhalation technique. Numerous studies have shown that patients’ inhaler technique is often poor, and this aspect of care is frequently neglected when a new drug is prescribed. Inhaler technique should be taught carefully when a new inhaler is introduced. Different devices require different techniques and both patients and healthcare professionals require training. Written or online materials are helpful to reinforce this, and reassessment and reinforcement of inhaler technique must be part of routine care.

Table 18.8.16 Inhaler technique: metered dose (MDI) vs. dry powder (DPI) devices

Metered dose inhalers	Dry powder inhalers
Shake inhaler	Prime device
Remove cap	Breathe out fully
Breathe out fully	Place in mouth
Place device in mouth	Rapid maximum inhalation
Start to breathe in steadily	Hold breath for a few seconds
Activate device	
Continue to breathe in steadily to maximum	
Hold breath for a few seconds	

The metered dose inhalers (MDI) combine drug with a hydrofluorocarbon propellant to produce an aerosol. Dry powder inhalers (DPI) are either pure drug or drug combined with a bulking agent to produce particles of the appropriate size. Worldwide, MDIs are the most commonly prescribed, and also tend to be easier to manufacture and cheaper. Some key elements of inhaler technique are outlined in **Table 18.8.16**. A key difference is that with MDIs a slow steady inspiration is required, whereas for DPIs a rapid inhalation is needed. In general, DPIs are easier to use and patient technique is more often correct with them than with MDIs. Of note, HFC propellants in MDIs are powerful greenhouse gases and are responsible for 4% of the United Kingdom NHS's entire carbon footprint.

MDI aerosols emerge at high speed, so even with the best inhaler technique the bulk of the material is actually swallowed rather than inhaled. To improve coordination, some MDIs are breath-actuated. Manual dexterity as well as coordinating breathing may be difficult for some patients. The use of a spacer device (**Fig. 18.8.35**) may as much as double lung deposition from MDIs as it allows the particles to slow down, hence their use is recommended for all long-acting MDIs and inhaled corticosteroids.

Bronchodilators

Although COPD is characterized by 'fixed' airflow obstruction, bronchodilator medications— β_2 -agonists and anticholinergic drugs—can act to relax airway smooth muscle and so reduce airway resistance (**Fig. 18.8.36**). In general the effect of these is smaller than is seen in bronchial asthma, but is clinically meaningful. In addition to usually modest improvements in FEV₁, bronchodilators also improve lung emptying, reducing lung volumes and dynamic hyperinflation. This can translate into improved symptoms and exercise capacity, even in patients whose FEV₁ does not improve with therapy, hence bronchodilator responsiveness testing by spirometry is not recommended to guide therapy. Bronchodilator use has not been shown to modify decline in lung function in COPD.

β_2 -Agonists

The main action of β_2 -agonists is to relax airway smooth muscle by stimulating β_2 -adrenergic receptors, which increase cAMP. Inhaled β_2 -agonists are preferred to oral preparations because they are as efficacious in much smaller doses and have fewer side effects. They have a relatively rapid onset of action and are therefore used for symptomatic relief, and they can also increase exercise tolerance in patients with COPD. The effects of short-acting β_2 -agonists (e.g.



Fig. 18.8.35 Spacer devices to improve drug deposition from metered dose inhalers.

salbutamol and terbutaline) last for 4–6 h. There is no evidence that the response to a β_2 -agonist diminishes with time, and patients with COPD should be told to take them as required, although those with severe disease may prefer to take regular doses three to four times daily to obtain symptomatic relief.

Long-acting β_2 -agonists (LABAs) can be given twice daily (such as salmeterol and formoterol) or once a day (indacaterol) due to their prolonged receptor occupancy. Formoterol and indacaterol have a more rapid onset of action than salmeterol. In randomized placebo-controlled studies LABAs have been shown to improve

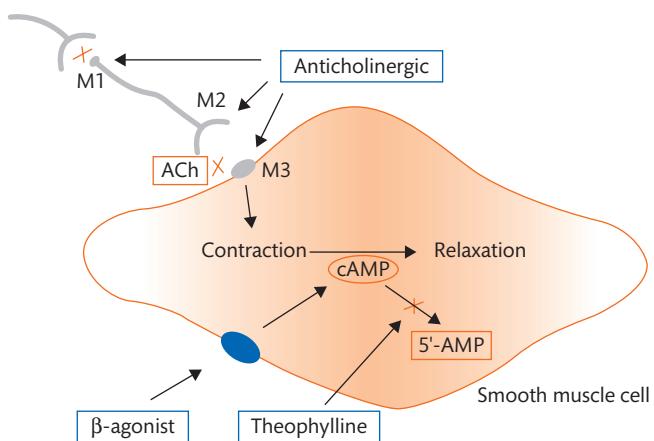


Fig. 18.8.36 Mechanisms of action of bronchodilators. Anticholinergics block muscarinic receptors so that acetylcholine is unable to act upon them; β -agonists increase levels of cAMP; theophylline blocks conversion of cAMP to 5'-AMP. M1, M2, and M3 are three distinct types of muscarinic cholinergic receptors. ACh, acetylcholine.

symptoms, FEV₁, quality of life, and to reduce exacerbation rates. They have no effect on rate of decline in FEV₁ or mortality. Newer LABAs include olodaterol and vilanterol.

Side effects of treatment with β₂-agonists include tachycardia and tremor, as well as the potential to precipitate cardiac rhythm disturbances in susceptible patients, although this is uncommon with inhaled therapy except when high doses are used via a nebulizer. In this context, particularly in older patients, hypokalaemia can occur. These effects show tachyphylaxis, unlike the bronchodilator actions. There is little evidence to support the use of sustained-release oral β₂-agonists (bambuterol) in patients with COPD and they are not recommended.

Anticholinergics

Anticholinergic drugs block the effect of acetylcholine on muscarinic receptors. Like β₂-agonists, short-acting anticholinergics (e.g. ipratropium and oxitropium) affect both central and peripheral airways, and also reduce functional residual capacity. They take 30 to 60 min to reach peak effect in most patients with COPD, which is slower than β₂-agonists, but their duration of action is longer (6–10 h).

Tiotropium bromide is an anticholinergic agent that has greater selectivity for M 1 and M 3 muscarinic receptors, and has a longer time course of action so can be given once daily. Tiotropium and similar long-acting antimuscarinic agents (LAMAs) improves symptoms, health status, decrease lung overinflation, improve the effectiveness of pulmonary rehabilitation, and decrease exacerbation rates in patients with COPD (Fig. 18.8.37). As with LABAs, LAMAs have not been convincingly shown to alter the progression of lung function decline.

Anticholinergics are poorly absorbed, which limits systemic side effects with inhaled preparations. The main side effect is dry mouth. Data from trials does not suggest that tiotropium increases cardiac risk, but caution is suggested in people with unstable cardiac disease as this population were excluded from trials.

Several newer long-acting antimuscarinic agents (LAMAs)—aclidinium bromide, glycopyrronium, and umeclidinium—have become available.

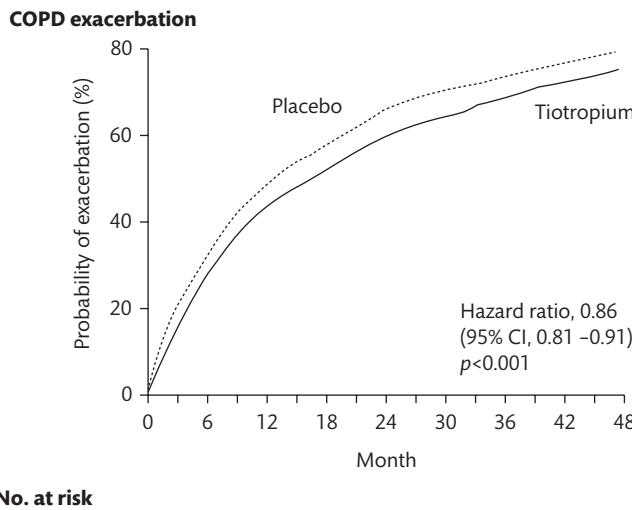


Fig. 18.8.37 Tiotropium reduced exacerbations of COPD in the UPLIFT trial. There were also fewer deaths in the treatment arm ($p = 0.09$).

Reproduced from Tashkin DP, et al. (2008). A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*, 359, 1543–54. Copyright © 2008, Massachusetts Medical Society.

Table 18.8.17 Considerations around new long-acting inhaled therapies

The effects of LAMAs and LABAs are likely to be class effects with few important differences between drugs
New combinations have become available in single devices (e.g. LAMA/LABA combinations)
Switching between drugs in a class is unlikely to be of general benefit, although may sometimes help an individual who is intolerant of a particular drug
Newer inhalers tend to be introduced at lower prices than existing ones to capture market share
Consideration of costs to the healthcare system must include time taken to teach and maintain inhaler technique
Molecules in longer use (formoterol, salmeterol, tiotropium) have a longer safety record
Newer delivery devices may or may not be preferred by individual patients, who may or may not find them easier to use correctly

Within the classes of both LABAs and LAMAs, there are few comparative data to guide selection between molecules. Licensing studies confirm that these drugs improve lung function and symptoms as well as reducing exacerbations, but have generally compared them to placebo rather than existing members of the same class (Table 18.8.17). The two classes of bronchodilator have different mechanisms of action, so their effects are complementary. Dual use is associated with reduced exacerbation risk, reduced breathlessness and increased quality of life and is therefore preferred first line therapy in the absence of features suggesting steroid responsiveness.

Inhaled corticosteroids

Inflammation in COPD is relatively nonresponsive to corticosteroids, particularly when compared to asthma. There is, however, evidence that inhaled corticosteroids (ICS) can improve lung function and reduce exacerbation frequency, both alone and in combination with a LABA in trials such as ISOLDE and TORCH, and with a LAMA. Mean effects were modest and it is likely that there are distinct steroid responsive and nonresponsive phenotypes within COPD. Although these cannot be precisely delineated features suggesting steroid responsiveness include any previous, secure diagnosis of asthma or of atopy, a higher blood eosinophil count, substantial variation in FEV₁ over time (at least 400 ml) or substantial diurnal variation in peak expiratory flow (at least 20%).

Early clinical trials of ICS used high doses in order not to miss an effect through underdosing. A consequence of this is that the licensed doses tend to be high. In COPD, moderate dose ICS (800 µg beclomethasone dipropionate (BDP) equivalent) has a similar clinical efficacy to very high dose ICS (2000 µg BDP equivalent). ICS in combination with long-acting bronchodilators are recommended for patients with frequent ($\geq 2/\text{yr}$) exacerbations and in those with more severe disease (FEV₁ < 50% predicted; see Fig. 18.8.38). The effects of inhaled corticosteroids are attenuated by smoking.

Side effects include oral thrush and bruising. Patients should be advised to gargle and spit out after using ICS to reduce absorption. Although ICS reduce exacerbations they are associated with an increased risk of pneumonia, which is dose related and therefore more of an issue with high potency molecules like fluticasone. (Fig. 18.8.39). High doses of ICS are also associated with adrenal suppression (Fig. 18.8.40).

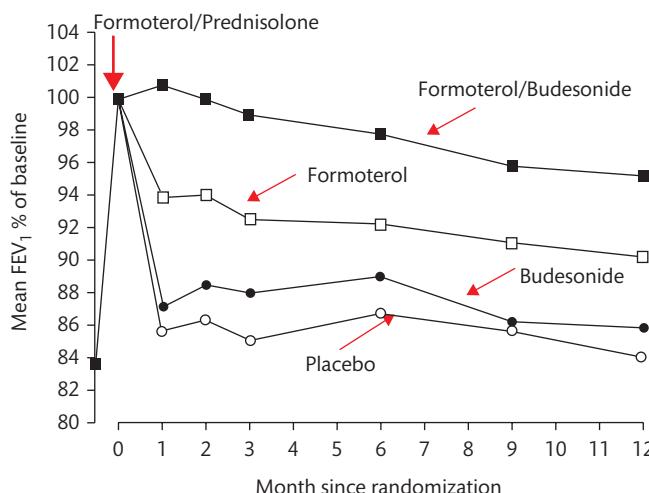


Fig. 18.8.38 Combinations of ICS and LABA had a bigger impact on FEV₁ than either component alone.

Reproduced with permission of the © ERS 2018: *European Respiratory Journal* Dec 2003, 22(6), 912–19; DOI: 10.1183/09031936.03.00027003.

Strategy for use of inhaled therapies

A strategy for use of inhaled therapies for stable COPD is shown in Fig. 18.8.41.

Oral corticosteroids

Oral corticosteroids are used for the treatment of acute exacerbations in COPD. Long-term oral steroid use is associated with systemic side effects including osteoporosis, weight gain, myopathy, and diabetes as well as increased mortality. The term ‘maintenance steroids’ should be avoided as there is little evidence that steroids ‘maintain’ COPD patients and it tends to encourage their use.

Oral steroid trials (e.g. prednisone 30 mg/day for 14 days) are sometimes used for diagnostic purposes: a large response may suggest a diagnosis of asthma, but should not be used to guide treatment decisions as the ISOLDE study showed clearly that the response to a 2 week prednisone trial did not predict subsequent response to ICS.

Other drugs

Theophyllines

Theophyllines, or methylxanthine derivatives, produce a modest bronchodilator effect in patients with COPD. There is still controversy over their exact mode of action: they may act as nonselective phosphodiesterase inhibitors, producing bronchodilatation by increasing cAMP, but anti-inflammatory effects have also been proposed. Many patients are unable to tolerate them because of nausea which unfortunately cannot be predicted in advance of a therapeutic trial.

Theophyllines are usually administered orally in chronic disease, or intravenously during acute exacerbations. They have a relatively narrow therapeutic index and monitoring of blood levels should be considered (therapeutic range for bronchodilator effects 10–20 mg/l). Slow release oral preparations are preferred, and prescription should be by specific preparation. Toxic effects include tremor, convulsions, and arrhythmias. Other anti-inflammatory theophylline effects may occur at lower doses. It had been proposed that low-dose theophylline will improve corticosteroid sensitivity via histone deacetylase (HDAC). However a large trial (TWICS) found no benefit from this.

Theophylline levels are reduced by smoking and doses may therefore need to be reduced when patients quit. Antibiotics, in particular ciprofloxacin, increase levels and oral doses should be halved if this antibiotic is used.

The possible beneficial effects of theophyllines have to be balanced against their potential side effects and toxicity. This means that they are usually reserved for patients with more severe disease in whom other treatments have failed to control symptoms adequately.

Phosphodiesterase 4 inhibitors

Phosphodiesterase 4 (PDE4) inhibitors, like theophyllines, also inhibit the breakdown of cyclic AMP and should therefore reduce inflammation. Roflumilast is an oral PDE4 inhibitor given once daily which has been shown to improve FEV₁ in patients already receiving treatment with a long-acting bronchodilator. Roflumilast also reduced the frequency of moderate to severe exacerbations in patients with severe to very severe COPD who were chronic sputum producers (chronic bronchitis) and who had a history of exacerbations. It may therefore have a role as an add on therapy to patients with these characteristics to reduce exacerbations. Trials to date have not, however, added it to patients with this phenotype already established on ‘triple therapy’ with a LAMA, LABA, and ICS.

Use of PDE4 inhibitors is limited by side effects. The most important of these are nausea, reduced appetite, abdominal pain, diarrhoea, sleep disturbance, and headache. Significant weight loss is common and hence Roflumilast should not be given to patients who are underweight, and it should be given with caution in patients with depression. It should not be used with theophyllines.

Long-term antibiotics

Recent studies have renewed interest in the use of antibiotics to prevent exacerbations, although concerns remain around value, possible side effects, and the development of drug resistance. The best data are for macrolide antibiotics, with studies of both erythromycin and azithromycin. A study by the US COPD Clinical Research Network randomized 1142 high risk COPD patients to receive azithromycin, at a dose of 250 mg daily (570 participants), or placebo (572 participants) for 1 year in addition to their usual care. The median time to the first exacerbation was 266 days (95% CI, 227–313) for

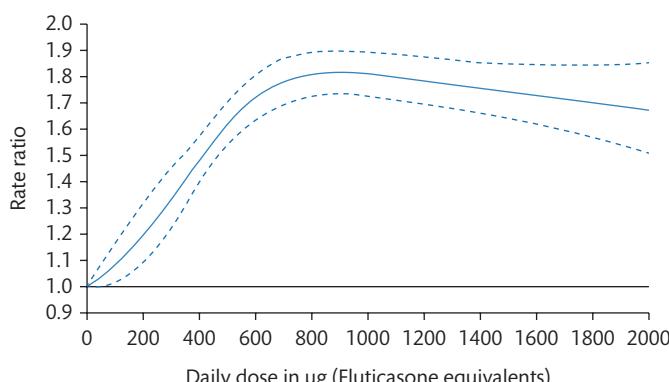


Fig. 18.8.39 Effect of fluticasone dose on pneumonia in patients with COPD.

From Suissa S, et al. (2013). Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*, 68, 1029–36.

When should you give an inhaled corticosteroid card?

Inhaled corticosteroids ≤ 800 micrograms (BDP Equivalent)/day				
Steroid	Proprietary	Dose/inhalation	Daily dose used	Cost/month
Beclometasone (BDP)	Asmabec, Clenil	50	2 twice a day	£ £
Beclometasone (BDP)	Asmabec, Pulvinal EasyHaler-BDP, Becodisk, Clenil	100	2 twice a day	£ £ £ £ £ (refill) £
Beclometasone HFA	Qvar	50	2 twice a day	£
Budesonide	Pulmicort 100, Easyhaler-BD	100	2 twice a day	£ £
Fluticasone	Flixotide 50 Accuhaler, Flixotide 50 Evohaler	50	1-2 twice a day 1-2 twice a day	£-££
Fluticasone	Flixotide 100 Accuhaler	100	1 twice a day	£
Fluticasone	Flixotide 125 Evohaler	125	1 twice a day	££
Ciclesonide	Alvesco	80	1-4 a day	£-£££
Mometasone	Asmanex	200	1 once a day	££
Beclometasone HFA/Formoterol	Fostair	100/6	1 twice a day	££
Budesonide/Formoterol	Symbicort 100	100/6	2 twice a day	£££
Budesonide/Formoterol	Symbicort 200	200/6	1 twice a day*	££
Fluticasone/Salmeterol	Seretide 50 Evohaler	50/25	2 twice a day	££
Fluticasone/Salmeterol	Seretide 100 Accuhaler	100/50	1-2 twice a day	££

Inhaled corticosteroids 800-1000 micrograms (BDP equivalent)/day				
Steroid	Proprietary	Dose/inhalation	Daily dose used	Cost/month
Beclometasone (BDP)	Clenil	200	2 twice a day	£
Beclometasone (BDP)	Pulvinal, EasyHaler-BDP, Becodisk	200	1 twice a day	££ ££ £££ (refill)
Beclometasone HFA	Qvar	100	2 twice a day	££
Budesonide	Pulmicort 200, Easyhaler-BD, Budefin	200	2 twice a day	££ ££ ££ (refill)
Budesonide	Pulmicort 400, EasyHaler-BD	400	1 twice a day	££ ££
Fluticasone	Flixotide 100 Accuhaler	100	2 twice a day	££
Fluticasone	Flixotide 125 Evohaler	125	2 twice daily	£££
Fluticasone	Flixotide 250 Accuhaler	250	1 twice daily	£££
Ciclesonide	Alvesco	160	2-3 once a day	££-£££
Mometasone	Asmanex	200	2 once a day	£££
Mometasone	Asmanex	400	1 once a day	££-£££
Beclometasone HFA/Formoterol	Fostair	100/6	2 twice a day	£££
Budesonide/Formoterol	Symbicort 200	200/6	2 twice a day*	££££
Budesonide/Formoterol	Symbicort 400	400/12	1 twice a day**	££££
Fluticasone/Salmeterol	Seretide 125 Evohaler	125/25	2 twice a day	££££
Fluticasone/Salmeterol	Seretide 250 Accuhaler	250/50	1 twice a day	££££

Inhaled corticosteroids >1000 micrograms (BDP equivalent)/day				
Steroid	Proprietary	Dose/inhalation	Daily dose used	Cost/month
Beclometasone	Asmabec, Clenil	250	2-4 twice a day	££-£££ £-££
Beclometasone	Pulvinal, EasyHaler-BDP, Becodisk	400	2 twice a day	£££ £££ ££££ (refill)
Beclometasone HFA	Qvar	100	3-4 twice a day	££
Budesonide	Pulmicort 200, Easyhaler-BD, Budefin	200	3-4 twice a day	£££ ££ ££-£££ (refill)
Budesonide	Pulmicort 400, EasyHaler-BD	400	2 twice a day	££££ £££
Fluticasone	Flixotide 250 Evohaler	250	2 twice a day	££££
Fluticasone	Flixotide 500 Accuhaler	500	1 twice a day	££££
Ciclesonide	Alvesco	160	2 twice a day	££££
Mometasone	Asmanex	200	2 twice a day	£££££
Mometasone	Asmanex	400	1 twice a day	££££
Budesonide/Formoterol	Symbicort 200***	200/6	3-4 twice a day*	£££££
Budesonide/Formoterol	Symbicort 400***	400/12	2 twice a day**	£££££
Fluticasone/Salmeterol	Seretide 250 Evohaler	250/25	2 twice a day	£££££
Fluticasone/Salmeterol	Seretide 500 Accuhaler***	500/50	1 twice a day	££££

Approximate costs (April 2012): £ = <£10 ££ = £10-20 £££ = £20-30 ££££ = £30-40 £££££ = £40+

* Symbicort 200 is licensed for use as maintenance and relief therapy (SMART), and as adjustable maintenance dosing. The daily dose may vary between 1 inhalation twice a day, up to a maximum of 8 a day but in studies, the average daily dose was 3 inhalations a day.

** Maximum recommended dose of Symbicort 400 2 twice a day is for asthma only, for COPD, dose is 1 twice a day

*** Only Symbicort 200/400 and Seretide 500 Accuhaler are licensed for use in COPD. Any other combination inhaler does not currently have licence for COPD.

CORTICOSTEROID SAFETY CARD NOT REQUIRED

CORTICOSTEROID SAFETY CARD RECOMMENDED
(Especially if additional corticosteroids taken)

CORTICOSTEROID SAFETY CARD REQUIRED

London Respiratory Team



Fig. 18.8.40 When should COPD patients receive a corticosteroid warning card?

Produced by The London Respiratory Network, 2015.

azithromycin, vs. 174 days (95% CI, 143–215) for placebo ($p < 0.001$). There were 1.48 exacerbations per patient year in the azithromycin group, as compared with 1.83 per patient year in the controls. Of note, little evidence of treatment effect was observed in current smokers.

Azithromycin can be effective taken less frequently (250 mg three times per week rather than daily) and has fewer drug

interactions than erythromycin, but it is significantly more expensive. Caution is required in patients with a prolonged QTc, and liver function tests should be measured before it is started. The possibility of hearing impairment, which occurs less frequently at lower doses, should be mentioned to patients and they should stop medication and seek medical attention if they notice this or

Chronic obstructive pulmonary disease in over 16s: non-pharmacological management and use of inhaled therapies

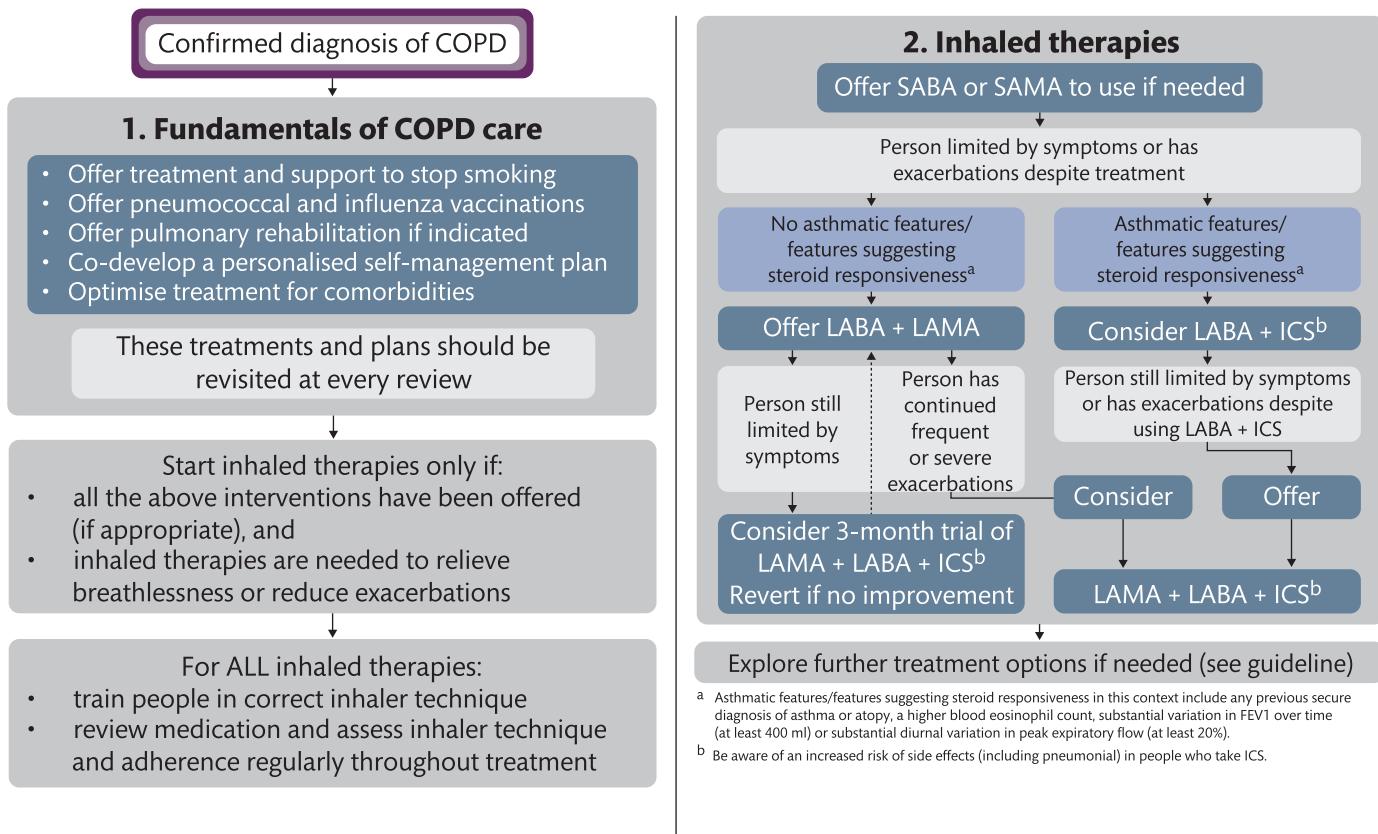


Fig. 18.8.41 Use of inhaled therapies for stable COPD.

NICE guidance on COPD, © Crown copyright 2019.

develop tinnitus. Caution is needed in the presence of atypical mycobacterial infections.

Pulsed therapy with moxifloxacin for 5 days every 8 weeks has also been shown to reduce exacerbations, but the use of quinolones in this way raises concerns as they are the only oral agents that can be used in pseudomonal infections.

Trials so far have followed patients up for 1 year only, so the longer term use of antibiotic remains a matter for clinical judgement. It should be remembered that COPD exacerbations cluster in time. Treatment may need to be indefinite, but depending on the individual patient response pauses in treatment in the summer or after a long period without exacerbations can be considered (Table 18.8.18).

Table 18.8.18 An approach to long-term oral antibiotics in COPD

Initiation	
Should a trial of oral antibiotics be considered?	Frequent exacerbations ($\geq 4/\text{yr}$) Life-threatening exacerbations Daily productive sputum Inhaled therapy optimized Other causes addressed (smoking cessation, chest physiotherapy, GORD, Vitamin D deficiency)
Are there cautions or contraindications?	Drug intolerance Prolonged QT interval on ECG Abnormal liver function tests Hearing impairment Atypical mycobacterial infection
Continuation	
Good response —exacerbations dramatically reduced in frequency. No longer significant daily sputum production,	Continue for one year, then consider pause over the course of the next summer and resume in winter
Moderate response —exacerbations modestly improved (e.g. still occurring but seem less severe)	Continue for one year, then consider pause over the course of the next summer
No response	Stop after 3 months

Mucolytics

Mucolytic agents are intended to reduce sputum viscosity and facilitate expectoration. Carbocisteine may reduce exacerbations in patients with milder disease, but overall effect size is small. In COPD patients with a chronic productive cough a trial of carbocisteine can be considered, but it should be stopped after 4 weeks if ineffective.

α_1 -antitrypsin

α_1 -antitrypsin replacement is feasible and in some countries offered as standard care. Evidence of benefit from trials is limited, although a recent study has shown that IV supplementation reduced decline in CT lung density, a measure of emphysema. However, it is not clear how this translates into clinical benefit, making estimations of the value of replacement (which is extremely expensive) difficult. Replacement therapy is not currently recommended in the United Kingdom.

Choice of medications

Medication for COPD should, as with other conditions, be chosen on the basis of evidence for efficacy, safety, and value. The London Respiratory Network key messages for Responsible Respiratory Prescribing are useful (Table 18.8.19).

Chest physiotherapy

Chest physiotherapy interventions can be useful in COPD to assist breathing control and improve sputum clearance. Techniques to assist breathing control include advice to slow expiration down and avoid breath stacking. Adopting postures which support the shoulders such as tripod sitting and wall leaning can be helpful to speed recovery from breathlessness (Fig. 18.8.42). Pursed lip breathing slows expiration and generates a positive pressure to reduce airway closure. It is not clear that teaching patients who do not do this spontaneously is helpful as it may simply focus attention on breathlessness. Small randomized controlled trials as well as larger cohort studies suggest that group singing training may be of benefit in COPD and this approach is becoming increasingly popular with patient groups.

Dynamic airway collapse can make it more difficult to clear sputum. Coughing harder, which generates increasing intrathoracic



Fig. 18.8.42 Breathing posture for COPD. Forward leaning breathing postures may be more comfortable for people with COPD.

pressure, may simply worsen this and is tiring. Techniques are often taught in the context of pulmonary rehabilitation and need to be tailored to the individual. In general, increased physical activity and the accompanying increase in respiration helps with sputum clearance, hence exercise is encouraged. Patients should understand that active and purposeful sputum clearance (e.g. morning and evening) will reduce the reservoir for infection to develop and should also reduce expectoration at other times.

All patients with chronic cough, irrespective of continence status, should be taught to contract the pelvic floor muscles before forced expirations and coughing. A key technique is 'huffing', which moves sputum from the small airways to the larger. This, combined with relaxed breathing control breaths and slow deep breaths, forms The Active Cycle of Breathing approach to mobilize sputum into larger airways making them easier to clear with less effort. This is particularly important in the management of patients with bronchiectasis: see Chapter 18.9 for further discussion.

Small, portable adjunct devices are sometimes used to facilitate sputum clearance. Oscillating positive expiratory pressure devices create positive expiratory pressure and oscillation during forced exhalation. This reduces premature airway closure and can help to mobilize secretions and reduce sputum viscosity. The Flutter® is a pipe-shaped device with a ball-bearing and the Acapella Choice® uses a counterweighted plug and magnet to create oscillation and positive pressure on expiration. The Cornet® is a flexible tube which deforms during exhalation causing vibration.

Hypertonic (7%) saline may be helpful in patients with viscous sputum. It occasionally causes bronchospasm, so when first administered patients should be supervised and spirometry should be measured before and after. Use of a predose bronchodilator may be helpful.

Table 18.8.19 Responsible respiratory prescribing—key messages

1 Respiratory medications are expensive
Doing the right things:
2. When prescribing any new respiratory inhaler, ensure that the patient has undergone NICE-recommended support to stop smoking
3. Pulmonary rehabilitation is a cost-effective alternative to stepping up to triple therapy and should be the preferred option if available and the patient is suitable.
Doing the right things right:
4. When prescribing any inhaled medication, ensure that the patient has undergone patient-centred education about the disease and inhaler technique training by a competent trainer
5. When prescribing an MDI (except salbutamol), ensure that a spacer is also prescribed and will be used
6. When prescribing high dose inhaled corticosteroids (>1000 µg BDP/day equivalent), ensure that the patient is issued with an inhaled steroid safety card

BDP, beclomethasone dipropionate; MDI, metered dose inhaler; NICE, UK National Institute for Clinical Excellence.

Table 18.8.20 Aspects of self-management in COPD

Having the ability to make changes to management without needing to consult a health professional
Understanding their symptoms
Explaining their condition to others
Smoking cessation
Maintaining and increasing physical activity
Ability to use physiotherapy techniques
Correct use of inhalers
Knowing when to contact health professionals

Self-management

Relating to the interventions and treatments considered above, patients with COPD should be encouraged and taught how to manage their condition (Table 18.8.20). There is evidence from systematic reviews that interventions including an action plan for worsening COPD symptoms improves health-related quality of life compared with usual care.

Lung volume reduction

Lung volume reduction surgery

Lung volume reduction surgery (LVRS; originally ‘reduction pneumoplasty’) involves resection of the most emphysematous part of the lung. These areas are the most compliant and therefore expand the most on inspiration, restricting the ventilation of healthier areas. The remaining lung, post-operation, is more elastic, improving ventilation and reducing V/Q mismatch. Reduced gas trapping also reduces operating volumes and thus improves the efficiency of respiratory muscles.

There are hazards associated with LVRS, including a risk of death and prolonged hospital stay due to complications such as air leak and pneumonia. A 1% mortality risk, with a 20% risk that the surgery will not lead to improvements, is typically quoted. Selection for LVRS requires a multidisciplinary approach including input from a physician, surgeon, and radiologist (Table 18.8.21).

The largest study of LVRS was the NETT in which 608 patients underwent bilateral LVRS and 610 continued with medical therapy alone. The trial identified a high risk phenotype in whom LVRS is unsafe; patients with FEV₁ less than 20% and either homogenous emphysema or TLco less than 20% predicted. LVRS was associated with a survival benefit in patients with low exercise capacity and upper lobe predominant emphysema (Fig. 18.8.43). Guidelines therefore recommend LVRS for patients with that phenotype.

Despite the established survival benefit very few procedures are done. In the United Kingdom an estimated 15 000 COPD patients might be eligible, but only about 100 operations per year are carried out. A BTS survey suggests that this is due to an exaggerated concern about procedural morbidity and the absence of structures to systematically evaluate possible patients for procedures. Case series suggest that modern practice is safer than at the time of NETT, with a unilateral approach and VATS being preferred, but in the United States only bilateral procedures are currently reimbursed by Medicare.

Bronchoscopic lung volume reduction approaches

Endobronchial valves, placed to occlude the airways leading to the worst affected lobe, allow air to leave but not enter, causing the target lobe to collapse. Response in early trials was highly variable, but where effective it appeared to be associated with a survival advantage. This was because valve placement is only beneficial if the interlobar fissures are intact. If the emphysematous process has damaged the fissures, collateral ventilation allows continued entry of air to the target lobe from the adjacent lobe and there is no effect. The BeLieVeR-HiFi study demonstrated that it is possible to identify responders prospectively, leading to improvements of a similar order of magnitude to LVRS. The eligibility criteria are similar to those for LVRS—heterogeneous emphysema with an appropriate target lobe, together with hyperinflation.

It is possible to measure collateral ventilation directly with the Chartis™ balloon catheter pressure and flow system. Computer scoring systems can characterize heterogeneity and also perform semi-automated assessment of fissure integrity. These approaches improve the success rate of the procedure.

The main complication is pneumothorax, which occurs in about 10% of patients. This can be delayed, but most occur within the

Table 18.8.21 General criteria when considering a lung volume reduction procedure

General criteria	<ul style="list-style-type: none"> significantly reduced exercise capacity lung function impairment (FEV₁ usually <50%) with significant hyperinflation (typically a plethysmographic RV >170% predicted) sufficiently well to cope with surgery prepared to accept some procedural risk (requires clinicians to be able to communicate this accurately) there is a ‘window of opportunity’ for intervention: in ‘end-stage’ patients it may be too late to intervene safely because lung function is too severely impaired, or because of frailty
Are they too well to consider intervention?	Lung function, exercise capacity, prognosis, MRC dyspnoea score <3.
Are they too unwell for intervention to be safe?	Lung function, frailty, exercise capacity <100 m, oxygen dependence.
Has treatment been optimized?	Smoking cessation, pulmonary rehabilitation, flu vaccination, inhaled and oral medication.
Is their lung function likely to rule out a procedure on safety grounds?	All three of FEV ₁ , TLco and Kco <20% predicted.
Do they have comorbidities that limit likely benefit or increase risk?	Pulmonary hypertension, unstable cardiac disease, malignancy, cerebrovascular disease. Ongoing smoking (possibility of intervention may help to promote quit attempts).
Have they ever had a CT thorax and, if so, has it been reported in terms of emphysema pattern?	Review existing CTs or obtain a CT if a potential candidate as above.

Review CT and lung function in MDT including respiratory physician, radiologist, and thoracic surgeon. Further investigations including echocardiogram, lung perfusion scan and a formal field exercise test (shuttle walk or 6 minute walk test) may be indicated.

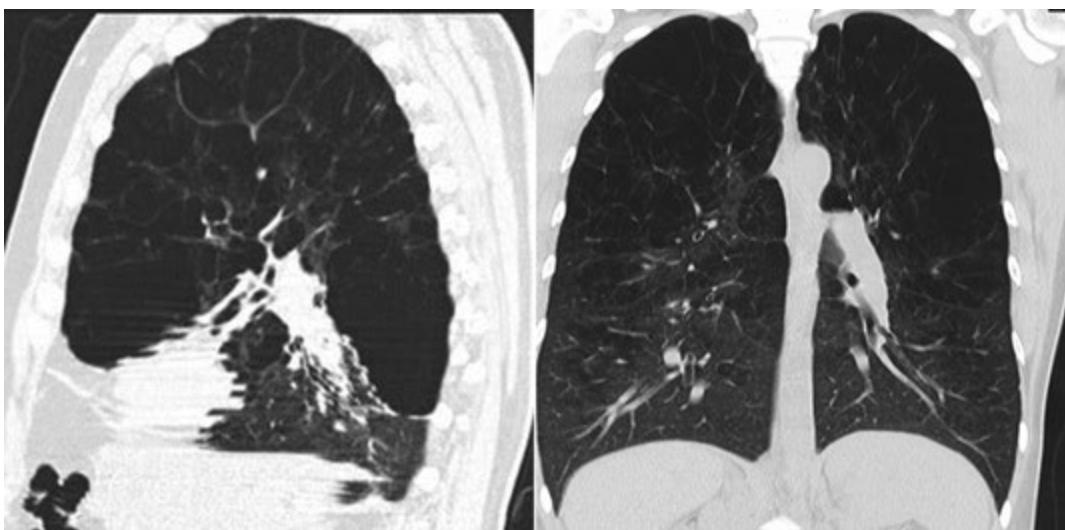


Fig. 18.8.43 Thoracic CT image showing upper lobe predominant emphysema in a pattern suitable for lung volume reduction surgery.

first 3 days and hence a period of in-patient observation is necessary. Pneumothorax usually improves with conventional intercostal tube drainage, but can be fatal. Because of the risk of complications, valve treatment is not recommended for people who are 'too frail' for LVRS to be considered.

Other techniques for inducing lung volume reduction include endobronchial coils, which restore the elastic recoil of the lung. Bilateral treatment is required, and clinical studies thus far suggest that this treatment approach may benefit a wider group of patients with emphysema (upper lobe predominant emphysema and more homogenous emphysema), but is not suitable for patients with severe bullous disease. Bronchoscopic thermal vapour ablation (using steam to cause scarring) and bronchoscopic targeted vagal nerve ablation are also under clinical investigation.

Oxygen supplementation

Supplemental oxygen in COPD is a treatment for hypoxia, not breathlessness, and is prescribed to improve survival and in some individuals to increase exercise capacity. Domiciliary supplemental oxygen therapy is usually considered in three categories:

- long-term controlled oxygen therapy for at least 15 h/day in patients with chronic respiratory failure;
- ambulatory oxygen therapy for exercise-related hypoxaemia;
- short-burst oxygen therapy—a palliative treatment for the temporary relief of breathlessness.

Continued cigarette smoking is a contraindication to long-term oxygen therapy because of the significant risk of fires, endangering both the patient and others. E-cigarettes are also a potential cause of combustion and should not be used with supplemental oxygen.

Long-term oxygen therapy

Long-term oxygen therapy (LTOT; administered for at least 15 hours/day) is indicated in patients with hypoxia defined as a PaO_2 less than 7.3 kPa on two occasions while stable at least three weeks apart, or between 7.3 and 8.0 kPa in the context of pulmonary hypertension or polycythaemia. These recommendations are based on

two multicentre trials, the MRC trial in the United Kingdom and the Nocturnal Oxygen Therapy Trial (NOTT) in the United States of America. The MRC trial of oxygen for 15 h/day showed an increase in 5-year survival from 25 to 41% (compared with no oxygen). The NOTT trial demonstrated the continuous use of oxygen therapy, with a mean use of 17.5 h/day, was beneficial in terms of survival, whereas use for only 12 h/day conferred no benefit (Fig. 18.8.44). Importantly, an absence of benefit has been demonstrated in trials of LTOT patients with less severe hypoxia, including those who desaturated at night but had daytime PaO_2 7.4–9.2 kPa, and those with a PaO_2 between 7.4 and 8.7 kPa.

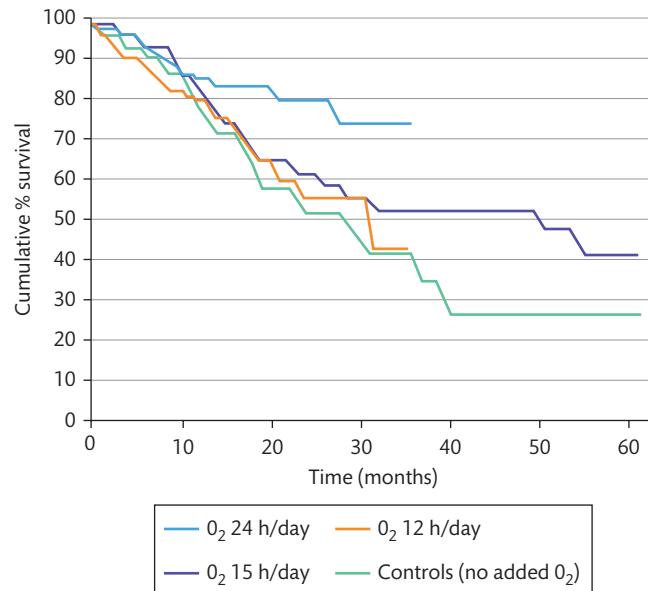


Fig. 18.8.44 Combined survival data from the NOTT and MRC studies of long-term oxygen therapy showing benefit in selected individuals. After *The Lancet*, 1981, **317**(8222), 681–6 and *Annals of Internal Medicine*, 1980, **93**(3), 391–8.

Benefit from LTOT is likely to be due in part to effects on pulmonary haemodynamics. Control subjects in the MRC trial experienced a 3 mm Hg/year increase in pulmonary arterial pressure, whereas this remained stable in the treated group. A reduction in polycythaemia may also be beneficial. The NOTT trial also found an improvement in cognitive function in the treated arm.

Oxygen can be delivered by mask, but nasal cannulae are usually preferred. Patients on LTOT should also receive a supply of portable oxygen to allow the patient to leave their home and to exercise without significant desaturation. Oxygen flow rates may have to be increased during exercise to maintain adequate oxygenation. Oxygen conserving systems, which are triggered by inspiration, deliver pulsed oxygen, and thus reduce total oxygen consumption. An important practical point is that flow rates from oxygen delivery devices may not match those from wall oxygen systems, so assessment of oxygen requirement should where possible be done using the same equipment as will be used at home.

Ambulatory oxygen

Ambulatory oxygen may improve exercise capacity in patients with COPD who desaturate during exercise. This should be evaluated formally for two reasons. Firstly, to avoid giving oxygen therapy to individuals who will not benefit, which is a significant source of waste. Secondly, a major issue with ambulatory oxygen is that many patients who receive it do not use it because of the weight, inconvenience, or stigma. A formal demonstration of improved exercise capacity can help to ensure compliance and should be considered in the context of more general advice to maintain or increase physical activity levels.

There is no evidence that oxygen provision in this context improves survival, although there may be a range of indirect benefits if individuals are able to remain more active and socially engaged.

Short-burst oxygen therapy to reduce breathlessness

Many patients on maximum drug therapy for COPD remain breathless on exercise, which has led to the use of oxygen to minimize the sensation of breathlessness. Studies of oxygen used in this way have failed to show any consistent effect on either breathlessness or the rate of recovery from breathlessness, and this may be a placebo effect. The use of short-burst oxygen therapy cannot be generally recommended in COPD.

Oxygen during air travel

Travel in commercial aircraft involves exposure to air pressurized to the equivalent of breathing 15% oxygen at sea level. This will worsen hypoxaemia and may lead to symptoms and increase the risk of vascular events. Although many patients travel safely without oxygen, the BTS guidelines on managing passengers with stable respiratory disease planning air travel recommend that a hypoxic challenge test be considered in COPD patients with severe disease ($\text{FEV}_1 < 30\%$) or where resting oxygen saturations are less than 95% breathing air. A hypoxic challenge test should also be considered in individuals who need ambulatory oxygen.

The hypoxic challenge test involves breathing 15% O_2 for 20 minutes. Supplemental oxygen will be required if PaO_2 falls below 6.6 kPa or O_2 saturation below 85%. Patients already receiving LTOT should receive double their usual flow rate while at altitude.

Table 18.8.22 Responsible oxygen prescribing for COPD

1. Oxygen is a treatment for hypoxia not breathlessness.
2. Oxygen is a medicine that should always be planned, prescribed, and reviewed by staff trained in oxygen prescription and use.
3. Acute oxygen prescription must include the target oxygen saturation range and state the appropriate interface and range of flow rates to achieve this. Oxygen saturations must be monitored according to an agreed management plan.
4. Long-term oxygen treatment (15–24 hours per day) should only be prescribed after specialist review and risk assessment.
5. Those who administer oxygen should have regular and ongoing training so that they are able to monitor and respond to a patient's oxygen saturations within an agreed management plan.
6. Patients who may benefit from ambulatory oxygen should have a specialist assessment with access to the full range of relevant equipment to meet their individual needs and maximize their independence.
7. Patients who smoke should not be prescribed long-term oxygen therapy. They should be offered clear communication of the reasons oxygen therapy cannot safely be offered to them while they smoke, individualized information about the benefits of smoking cessation for them, treatment for tobacco dependence, and planned follow-up.
8. Specialist oxygen assessment and follow-up should include individualized patient and carer education about oxygen treatment, comprehensive risk assessment, and carbon monoxide monitoring. Patients should be informed of their responsibility to use oxygen safely, including abstinence from smoking and of the reasons for this. Time should be allowed to check patients' understanding of this information.
9. Patients on long-term oxygen therapy at risk of harm from excessive oxygen should be identified and their care plan shared with their GP and local hospitals as well as ambulance and out of hours services.
10. Home Oxygen Service Assessment and Review services are vital to ensure evidence-based patient-centred care and optimal value for money, and these should be integrated with local respiratory services to be effective.

From the London Respiratory Network.

Oxygen prescribing

Guidelines for responsible prescribing of oxygen in patients with COPD are shown in Table 18.8.22.

Noninvasive ventilation

Noninvasive ventilation (NIV) has a well-defined place in the management of decompensated hypercapnic (Type II) respiratory failure. Its role in stable COPD is less clear. Trials have been small and often evaluated ineffective NIV strategies that have not appreciably reduced CO_2 levels. It is appropriate to consider domiciliary NIV in patients with symptomatic hypercapnia—morning headaches and drowsiness. Domiciliary NIV may also be beneficial, reducing exacerbations and healthcare costs, in those who have required NIV on multiple hospital admissions. However, a strategy of starting all patients admitted to hospital who required acute NIV on long-term NIV did not improve outcomes, presumably because in many the hypercapnia does not persist.

A German study recruiting COPD patients with a PaCO_2 above 7 kPa evaluated NIV adjusted to target at least a 20% reduction in PaCO_2 or a value below 6.5 kPa and found that this did improve survival. This needs to be balanced against the impact on quality of life which NIV may have. Tolerance of NIV varies between individuals and any NIV service requires significant expertise and technical support to ensure optimization of ventilator settings and that issues

such as mask fit and patient education are addressed. The HOT-HMV trial found that NIV was of benefit in patients whose type II respiratory failure persisted after hospital discharge.

Bi-level ventilation is also sometimes required in COPD patients who also have obstructive sleep apnoea.

Lung transplantation

Lung transplantation, which is discussed in Chapter 18.16, should be considered in selected patients with very advanced COPD and a life expectancy of less than 2 to 3 years, where it has been shown to improve quality of life and functional capacity. Outcomes are poor in people over 60, both because they are less able to cope with the stress of surgery and because they have increasing rates of multimorbidity which are aggravated by the antirejection therapies needed post-transplant.

Palliation and end-of-life care

Many patients with COPD remain very symptomatic despite therapy, with health status equivalent to or worse than many common malignancies. Common issues are breathlessness, anxiety, and exacerbations (Table 18.8.23). Attention to optimizing care with smoking cessation support, pulmonary rehabilitation, and inhaled and other therapies is important. Social isolation and poverty are also frequent issues, and historically COPD patients have missed out on palliative care services.

There is evidence that patients who use a hand-held battery-powered fan to blow air onto their face experience significant symptomatic relief. Low dose oral morphine (e.g. 2.5–5 mg twice per day) can be effective in patients with severe breathlessness: dependence and respiratory depression are not issues, although a laxative should be prescribed to prevent constipation. Anxiety attacks which are not controlled with nonpharmacological interventions may respond to sublingual lorazepam.

Prognostication is difficult in COPD. The pattern of background decline mixed with acute exacerbations and recovery makes disease trajectory less easy to track than in malignancy. In addition, the picture is complicated by comorbidities. Only about a third of COPD patients die from COPD, with cardiovascular causes and malignancy common. There are many prognostic scores which are useful for stratifying populations but of limited use for individual patients.

Table 18.8.23 Palliative care and end-of-life interventions in COPD

	Palliative interventions
Breathlessness	Pulmonary rehabilitation Optimize inhaled medication—prescription and use Specific breathing control advice Hand-held battery-powered fans Low dose morphine
Anxiety	Pulmonary rehabilitation Specific breathing control advice Talking therapies/Cognitive behavioural therapy Low-dose lorazepam Discuss anxieties about
End-of-life issues	Advanced directives Consider ceilings of care (e.g. NIV but not intubation) End-of-life tasks—wills, and so on.

The question ‘would you be surprised if this patient died in the next 12 months’ can be a useful trigger for considering end-of-life care discussions, which need to be handled sensitively. Family members are often unaware of how severe a patient’s condition is. Discussion of ceiling of care may be appropriate (e.g. NIV but not intubation).

Multimorbidity and COPD

The presence of multiple long-term conditions has become the norm rather than the exception as people age. A cross-sectional study from a database of 1 751 841 people registered with 314 medical practices in Scotland found that fewer than one in five people with COPD only had COPD. COPD, being a disease of ageing associated with smoking, reduced physical activity, an adverse early life environment and lower socioeconomic status, shares many risk factors with other chronic conditions which frequently co-occur, including cardiovascular disease, osteoporosis, cognitive impairment, and psychological problems. Comorbidities may represent a common susceptibility to risk factors or a systemic ‘overspill’ of lung inflammation impacting directly on remote disease processes, such as the development of atherosclerosis. Importantly, the patterns of comorbidities is associated with deprivation. The most deprived patients with COPD commonly display a cluster of coronary artery disease, depression, and chronic painful conditions (Fig. 18.8.45).

Cardiovascular disease

Data from UK primary care found that a diagnosis of COPD was associated with a 10.1-fold increase in risk of myocardial infarction and a 3.4-fold risk of stroke. Acute exacerbations of COPD are a high risk. Raised troponin, an indicator of cardiac damage, is frequently observed during hospital admission and is associated with increased mortality. Management of vascular disease should be along conventional lines. Historically there has been reluctance to use β -blockers in people with airway disease because of the risk of acute bronchospasm in asthma. However, β blockade appears to be generally safe in COPD patients with cardiac disease, and associated with a survival benefit. A cardioselective agent should be used, at a low dose initially and then titrated up, as necessary.

Atrial arrhythmias occur commonly as a complication of COPD. They may be triggered by exacerbations and may be transient. Management is conventional. As with all patients, bronchodilator therapy should be optimized, avoiding excessive doses which contribute to tachycardia without additional symptomatic benefit. Nebulized bronchodilators and corticosteroids may contribute to electrolyte abnormalities, which should be corrected.

Osteoporosis

Osteoporosis is a common COPD comorbidity. Loss of bone density is accelerated by smoking and physical inactivity as well as being aggravated by corticosteroid treatment. Poor nutrition is common in COPD and reduced time spent outdoors mean that vitamin D deficiency is also common. Treating frank vitamin D deficiency has been shown to reduce exacerbation frequency. Osteoporotic vertebral collapse is particularly problematic in COPD as it can lead to restriction of the chest wall. Osteoporotic rib fractures due to coughing or other trauma can also impede respiration.

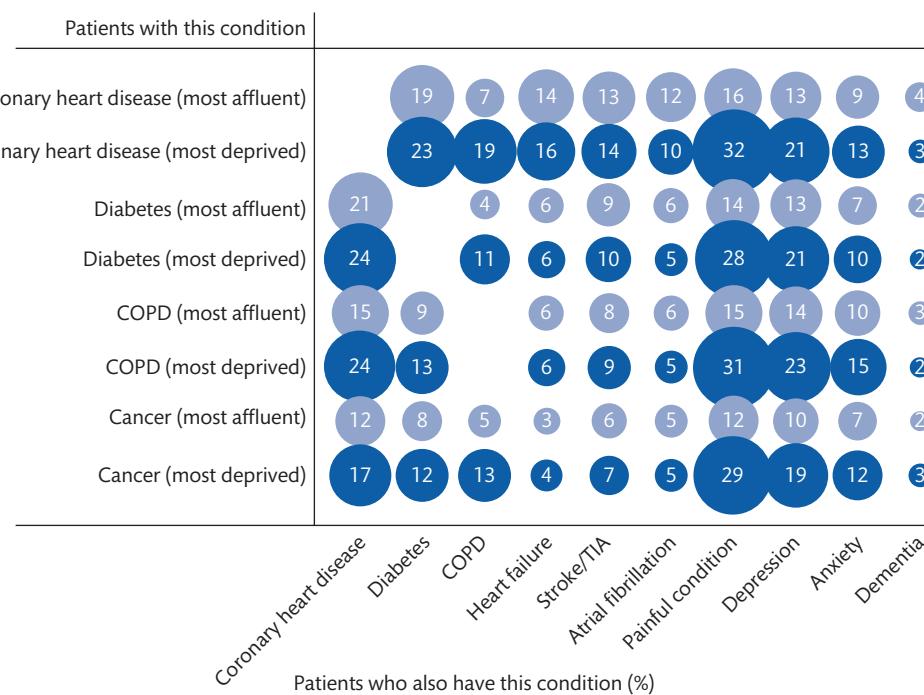


Fig. 18.8.45 Patterns of multimorbidity in COPD and association with deprivation.

From Barnett K, et al. (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*, 380(9836), 37–43.

Cognitive, psychological, and nervous system problems

Many patients with COPD are anxious or depressed. This may be reactive in response to the symptoms and limitations of the disease and without any specific features. Screening by systematic use of a tool such as the Hospital Anxiety and Depression Score as part of an annual 'comprehensive clinical and psychosocial assessment' may be recommended. Beyond being a determinant of the content of depressive thoughts, COPD itself makes little difference to the management of depression. Exercise, talking therapies, and pharmacotherapies are used as appropriate. An overlap between anxiety and breathlessness can be addressed through pulmonary rehabilitation and learning techniques for breathing control such as pursed lip breathing. PR in part functions as a form of graded exposure to breathlessness. There is evidence from fMRI that pulmonary rehabilitation is associated with altered neural responses related to learned breathlessness associations.

Mild cognitive impairment related to hypoxia, which may particularly affect information processing and verbal memory, has been described in COPD. This can impact on the understanding and use of self-management plans, and should be considered if new inhaler devices are being introduced during acute exacerbations.

Peripheral neuropathy (including increased phrenic nerve conduction time) is frequently observed in COPD and increased excitability of the diaphragm motor cortex has been reported. COPD patients frequently describe muscle cramps, which are often attributed to the use of bronchodilators, though the aetiology is not clear.

smoking cessation, prompt treatment, avoiding unnecessary hospitalization, and enhancing recovery.

There are several definitions, but exacerbations are usually defined as episodes where there is a deterioration in symptoms that exceeds normal day to day variation and which prompt a change in treatment. This is an event-based definition dependent on behaviour. Studies using symptom diaries suggest that patients under-report exacerbations and also that nonreported exacerbations are associated with worse health status. The Anthonisen criteria are used to classify exacerbations based on symptoms (**Table 18.8.24**).

Frequent exacerbations are associated with worse health status and more rapid lung function decline. They also tend to cluster in time. Data from the ECLIPSE study suggests that the 'frequent exacerbator' is a relatively stable phenotype which can occur at any level of airflow obstruction, although exacerbations do become more common as lung disease progresses. This may be because of a reduction in functional reserve meaning that the threshold for exacerbation is reached more easily. This mechanism probably explains why bronchodilator treatments, despite having no direct effect on lung inflammation, reduce exacerbation rate.

Acute exacerbations of COPD are usually caused by infections, bacterial and viral, and are more common in individuals who are

Table 18.8.24 Anthonisen criteria for COPD exacerbations

Type I	Type II	Type III
All three symptoms: Increased sputum volume Increased sputum purulence Increased dyspnoea	Any two symptoms	One symptom together with one minor symptom/feature <ul style="list-style-type: none">• Recent upper respiratory tract infection• Increased wheeze• Increased cough• Fever

Management of acute exacerbations of COPD

Acute exacerbations of COPD are responsible for impaired quality of life and patient distress, as well as much of the healthcare resource utilization. Management focuses on prevention, in particular

chronically colonized. They can also be triggered by air pollution and cold temperatures, and approaches using Meteorological Office data to warn patients of increased risk have been proposed.

Inflammation in airway walls, together with increased mucus production, causes an increase in airflow obstruction and ventilation perfusion mismatch. This leads to dynamic hyperinflation, an increased work of breathing, and increased symptoms. Respiratory muscles may be unable to cope with the increased load, leading to respiratory failure.

Increased circulating inflammatory mediators, catecholamines, and hypoxia have systemic effects. Right-sided cardiac pressures increase and cardiac function is further restricted by hyperinflation. Atrial arrhythmias are common. These factors, together with immobility and corticosteroid treatment, contribute to acute loss of skeletal muscle bulk which delays recovery and also drives bone loss.

The initial approach to management should be to establish the diagnosis of acute exacerbation of COPD and to evaluate the severity of the exacerbation to decide on the best location for treatment (Table 18.8.25). The differential diagnosis includes cardiac failure, pulmonary embolism, and pneumothorax and pleural effusion.

It may be the case that specific exacerbation phenotypes can be identified which will guide stratified approach to therapy. For example, sputum eosinophilia is associated with steroid responsiveness.

In the community setting it is not necessary to obtain a chest X-ray or sputum if the diagnosis is clear. Many patients are able to self-diagnose acute exacerbations and self-manage with a rescue pack of antibiotics and steroids. This can reduce delays to the onset of treatment, although they should be encouraged to inform their medical team when they do this. Some individuals may delay treatment unnecessarily and some will make excessive use of rescue medication, so this needs to be kept under review. The use of three or more rescue packs should prompt a review to establish if treatment is appropriate and whether there is a reversible cause.

Having established a diagnosis of an acute exacerbation of COPD the key question is whether to manage the patient at home or in hospital. Roughly 20% of patients who would conventionally be admitted to hospital can be managed at home with an early supported discharge or admission avoidance scheme. These involve appropriately qualified health professionals reviewing and supporting patients at home daily for a limited period, with the provision of equipment such as nebulizers or short-term home oxygen, as necessary.

Criteria to guide clinical judgement are described in Table 18.8.26. Any decision to manage the patient at home should include a plan

Table 18.8.25 Features of acute exacerbation of COPD

History	Cough Sputum volume and purulence Haemoptysis Sleep disturbance Wheeze
Physical signs	Increased respiratory rate Use of accessory muscles Tachycardia Cyanosis Confusion Peripheral oedema
Investigations	Pulse oximetry Chest X-ray ECG Sputum for culture

Table 18.8.26 Where to manage the patient with an acute exacerbation of COPD

	Treat at home?	Treat in hospital?
Able to cope at home	Yes	No
Breathlessness	Mild	Severe
General condition	Good	Poor/deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral oedema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good	Lives alone/not coping
Acute confusion	No	Yes
Rapid rate of onset	No	Yes
Significant comorbidity (particularly cardiac disease and insulin-dependent diabetes)	No	Yes
SaO ₂ < 90%	No	Yes
Changes on chest X-ray	No	Present
Arterial pH level	≥ 7.35	< 7.35
Arterial PaO ₂	≥ 7 kPa	< 7 kPa

Based on NICE 2010 guidance on COPD management.

for the patient's review. The recently developed DECAF (dyspnoea, eosinopenia, consolidation, acidosis, and atrial fibrillation) score may be a useful guide for identifying individuals who can be discharged safely.

Outpatient management of AECOPD

Bronchodilator therapy is increased. In some cases this will require the use of nebulized bronchodilators.

Haemophilus influenzae, streptococcus pneumoniae, and moraxella catarrhalis are the most common bacterial pathogens, so empirical antibiotic treatment should cover these. Amoxicillin is first line in the United Kingdom, with doxycycline recommended for those who are allergic. In patients with multiple exacerbations and in those who fail to respond, sputum culture is advised to identify antibiotic resistance and detect the presence of pseudomonas aeruginosa which will not respond to usual broad spectrum antibiotics.

Oral corticosteroids (e.g. 30 mg or 0.5 mg/kg prednisolone/day) have been shown to accelerate recovery from acute exacerbations of COPD. Long courses are unnecessary: the minimum effective duration of treatment has not yet been defined, but 5 days' treatment is likely to be sufficient.

Management of patients admitted to hospital with AECOPD

Hospital admission with an acute exacerbation of COPD carries a significant adverse prognosis. The 2014 Royal College of Physicians/British Thoracic Society COPD audit found a 4.3% mortality rate during the index admission. Patients' usual level of breathlessness predicted in-hospital mortality: 8% for an MRC dyspnoea score of 5; 2.9% in MRC 4; 1.7% in MRC 3. Other factors associated with an increased risk of a poor outcome are previous hospitalization, age,

smoking status, comorbidities, hyponatraemia, hyperglycaemia, and a low eosinophil count.

Oxygen

Excessive oxygen therapy is harmful in acute exacerbations of COPD. This is a hazard that must be addressed by emergency departments and ambulance services. Patients with respiratory failure should be given controlled oxygen therapy (24–28%) through a venturi mask, or 1–2 litres by nasal prongs adjusted to achieve an O₂ saturation between 88 and 92%. In patients hospitalized with acute exacerbations of COPD arterial blood gases should be measured if saturations are below 95% on air.

Pharmacotherapy

Bronchodilator therapy should be increased and nebulized therapy may be required. Nebulizers should be air driven with supplemental oxygen by nasal cannula, as necessary. Corticosteroids should be given orally as in outpatient management, with intravenous administration only where patients are nil by mouth. Initial antibiotic therapy should also be as for community treatment.

Noninvasive ventilation

Clinical trials have demonstrated a dramatic impact on survival with bi-level NIV in patients with a decompensated respiratory acidosis (PaCO₂ > 6 kPa, pH < 7.35). Response should be assessed with repeat ABGs within one hour. The location of NIV treatment will vary according to the health system. With appropriate trained staff NIV can be delivered on a respiratory ward, but a high dependency environment may have advantages, allowing arterial line placement, the initiation (if indicated) of other supportive therapies such as inotropes, and safer use of sedation, which may be required in some individuals

who find it hard to tolerate NIV. When patients are commenced on NIV is important to ensure that there is a clear treatment plan if the NIV fails as to whether intubation is appropriate. It is not necessary to place a nasogastric tube routinely in patients undergoing NIV. NIV has rendered the use of respiratory stimulants (doxapram) obsolete.

Invasive mechanical ventilation

Acute mortality rates in patients with acute exacerbations of COPD who are intubated are no worse than for those with other medical conditions, although this represents a selected group of all those with respiratory failure. Complications include ventilator acquired pneumonia and acute lung injury as well as pneumothorax, and a tracheostomy may be necessary. Poor outcomes are common in patients who are housebound who may be forced to endure prolonged and ultimately unsuccessful attempts to wean. Intubation in this population can be considered to be futile. Patients in whom invasive mechanical ventilation is being considered are often semi-conscious, so it is helpful in this situation for the issues to have been discussed in advance such that a clear expression of the individual's wishes is available.

Acute exacerbations of COPD are associated with immobility and an inflammatory response, hence venous thromboembolism prophylaxis should be administered. Corticosteroids and β₂-agonists may cause hypokalaemia and this and other electrolyte disturbances should be monitored for and corrected. Physiotherapy input to assist early mobilization may be beneficial, but evidence does not support routine chest physiotherapy in acute exacerbations of COPD to assist sputum clearance.

A care bundle approach to discharge (Fig. 18.8.46) has been suggested to systematize care, with some evidence that

Inform the COPD CNS of all COPD patients within **24 hours of arrival** including patients discharged. Extension _____

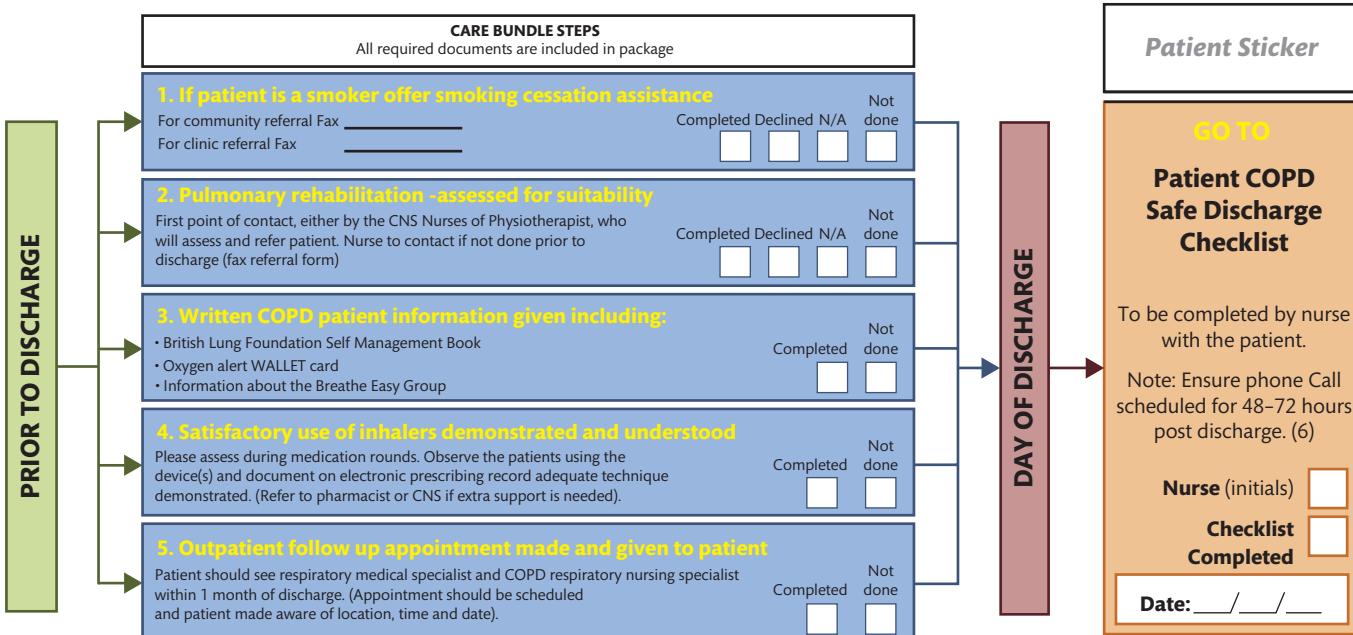


Fig. 18.8.46 COPD discharge care bundle. This care bundle is a group of evidence-based items that should be delivered to all patients being discharged from hospital following an acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The care bundle aims to improve quality of care, patient experience, and minimize the risk of re-hospitalization.

Adapted from Hopkinson NS, et al. (2012). Designing and implementing a COPD discharge care bundle. *Thorax*, 67, 90–2.

COPD SAFE DISCHARGE CHECKLIST British Lung Foundation (BLF) 08458 505020 www.lung.org To find your local Breathe Easy Group 08458 505020 www.lunguk.org/supporting-you/breathe-easy NHS Out Line 0800 0224332	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Name: _____</td> <td style="width: 50%;">Hospital Number: _____</td> </tr> <tr> <td>Date: _____</td> <td>DOB: _____</td> </tr> <tr> <td colspan="2" style="text-align: center; padding: 10px;"> This plan is for people who are going home after coming to hospital with a 'flare up' or 'exacerbation' of COPD (chronic obstructive pulmonary disease) </td> </tr> <tr> <td colspan="2" style="text-align: center; padding: 5px;"> We want to make sure that you can manage safely at home. </td> </tr> <tr> <td colspan="2" style="text-align: center; padding: 5px;"> Before you go home you should be able to tick all of these boxes. If not you must ask one of the ward nurses to help. </td> </tr> <tr> <td colspan="2" style="text-align: right; padding: 5px;"> Tick Here </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> You should feel able to use your inhalers, and other medications including steroids properly. </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> The nurses have actually watched you use your inhalers, and spacer if appropriate, to make sure that you are doing it correctly. </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> The benefits of pulmonary rehabilitation have been explained to you and you have been offered the chance to take part in a course if appropriate. </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> If you are a smoker you should have been offered assistance to quit. </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> You should know what the plan for your follow up care is. </td> </tr> <tr> <td colspan="2" style="padding: 5px;"> You should have received written information explaining about COPD. </td> </tr> </table>	Name: _____	Hospital Number: _____	Date: _____	DOB: _____	This plan is for people who are going home after coming to hospital with a 'flare up' or 'exacerbation' of COPD (chronic obstructive pulmonary disease)		We want to make sure that you can manage safely at home.		Before you go home you should be able to tick all of these boxes. If not you must ask one of the ward nurses to help.		Tick Here		You should feel able to use your inhalers, and other medications including steroids properly.		The nurses have actually watched you use your inhalers, and spacer if appropriate, to make sure that you are doing it correctly.		The benefits of pulmonary rehabilitation have been explained to you and you have been offered the chance to take part in a course if appropriate.		If you are a smoker you should have been offered assistance to quit.		You should know what the plan for your follow up care is.		You should have received written information explaining about COPD.	
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You should know what the plan for your follow up care is.																									
You should have received written information explaining about COPD.																									

Once you are home

1. Hopefully your condition will improve steadily. If you feel that you are getting worse or that your breathing is disturbing your sleep then get in touch with your GP or community COPD team promptly.
GP number: _____
2. If you are on a course of antibiotics or steroids it is important to complete them even though you may feel better.
3. You should have a follow up appointment within a few weeks of going home to review your care.
4. Somebody from the hospital or the community team should be in touch in the first few days after you go home to see that you are getting on OK.
Tick if you **do not** want to receive this phone call

My phone number is: _____ Preferred time to call: _____

Health Professional (Print and Signature): _____ Patient Name: _____

Patient Signature: _____

Fig. 18.8.47 COPD safe discharge checklist.

Adapted from Hopkinson NS, et al. (2012). Designing and implementing a COPD discharge care bundle. *Thorax*, 67, 90–2.

implementation is associated with a reduced rate of readmissions. Items included are smoking cessation, assessment for post-exacerbation pulmonary rehabilitation, inhaler technique, the provision of written information and arranging follow-up. Close liaison between hospital and community teams is important for continuity. Although there is variation in readmission rates, the extent to which hospitalization in frail patients with multiple comorbidities can actually be reduced is often exaggerated in discussions in this area.

A safe discharge checklist (Fig. 18.8.47) can also be used, signed by both the discharge nurse and the patient, to ensure that these important steps have been carried out and to reinforce their implementation within the system.

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