COPD

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COPD, Phenotypes, and Endotypes

Chronic obstructive pulmonary disease (COPD) is a problematic name. It has replaced earlier terms such as chronic obstructive airways disease (COAD) and chronic obstructive lung disease (COLD). In the United Kingdom, NICE (National Institute for Health and Care Excellence) guidelines use a lengthy definition which commences "COPD is characterised by airflow obstruction that is not fully reversible. The airflow obstruction does not change markedly over several months and is usually progressive in the long term. COPD is predominantly caused by smoking" [1]. This definition causes difficulty as it is based around a single physiological variable (airflow obstruction) which is common to other conditions such as asthma and bronchiectasis, and although it recognises smoking as a cause, only a minority of smokers develop the disease. Further, the full definition goes on to recognise the importance of inflammation as an underlying mechanism, but is only able to define this imprecisely and by its difference from asthma.

Some years ago, lumping together COPD as a single entity was a useful public relations exercise. Despite high prevalence and mortality, COPD was relatively neglected in public health terms. The unitary label allowed initiatives such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) to focus healthcare efforts worldwide [2]. However, COPD includes chronic bronchitis, emphysema, and small airways disease in varying amounts, giving differing clinical presentations.

Classically these were recognised as the "pink puffer" who was thin, normoxic, and breathless, with predominant emphysema, and the "blue bloater" who was obese, hypoxic, and less breathless, but with cor pulmonale. Though patients fitting these classical definitions are seen, this division fell into disrepute as the link between phenotype and underlying pathological abnormality was inconsistent and the distinction failed to offer different treatment options.

Later the concept of phenotypes resurfaced, with a wider recognition that COPD is associated with a range of different co-morbities and clinical presentations, and the sense that new treatment might need to be developed and used selectively in differing patient groups [3]. For instance, principle component and cluster analysis has been used to define four phenotypes within a cohort, using eight clinical characteristics, [4] which the authors describe as:

Phenotype 1: young subjects with predominant severe to very severe respiratory disease
Phenotype 2: older subjects with mild airflow limitation, mild symptoms, and mild age-related comorbidities

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Phenotype 3: young subjects with moderate to severe airflow limitation, but few comorbidities and mild symptoms
Phenotype 4: older subjects with moderate to severe airflow limitation and severe symptoms ascribed, at least in part, to major comorbidities (e.g. chronic heart failure)

Importantly, each phenotypic cluster contains subjects with similar values of FEV_1. NICE uses a classification based purely on measures of FEV_1, (Table 4.1) [1].

The NICE guidelines note that its classification was originally in line with GOLD guidelines, though subsequently these have been adapted to use a bivariate classification acknowledging symptoms and "risk" (Fig. 4.1) [2]. It is clear these limited, though pragmatic, classifications fail to address fully the diversity of phenotypes described and are likely to need to be revised in future, particularly as more targeted treatments for COPD are developed. An early instance is roflumilast, which seems to reduce exacerbations only in the COPD phenotype characterised by chronic sputum production [5].

More recently still, there has been a move beyond phenotypes. With the advent of proteomics it is recognised that a given phenotype may result from differing underlying mechanisms. A unitary underlying mechanism is defined as an endotype [6]. This has resulted in the uncomfortable realisation that traditional diagnostic boundaries between COPD and asthma may in fact be artificial, and that mechanistic understandings will make different distinctions allowing specific targeting of therapies [7]. Instead of the current practice of lumping COPD together, there is likely to be a splitting of airways disease according to mechanisms and treatable traits, for instance that associated with eosinophilic inflammation [8]. A number of large observational studies are currently in the process of reporting results, helping to forward understanding of phenotypes and

Table 4.1 Classification of COPD according to NICE (UK National Institute for Health and Care Excellence)

Stage	Classification	Range
1	Mild	FEV1 in the normal range (over 80%), but FEV1/FVC <0.7 (plus symptoms)
2	Moderate	FEV1 between 50% and 79%
3	Severe	FEV1 between 30% and 49%
4	Very severe	FEV1 under 30%

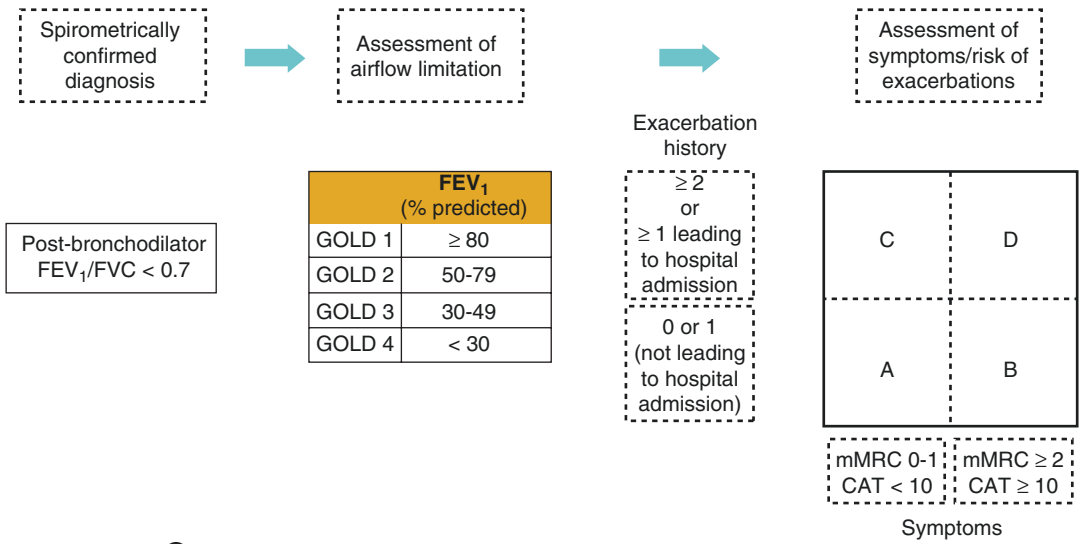

Fig. 4.1 GOLD classification of COPD. Used with permission from Global Initiative for Chronic Obstructive Lung Disease—GOLD

endotypes, with the promise of progress in the near future, with updated reports available on host websites [9].

History and Clinical Features

Chronic Lung Disease

The cardinal symptoms of COPD are breathlessness, cough (with or without sputum), with onset in middle or old age, usually in those with a significant smoking history. NICE guidelines suggest it should be considered in subjects aged over 35 years with a chronic cough and a smoking history [1]. It is important to be alert to the significance of these symptoms, which otherwise may be attributed to the effects of age, or dismissed as merely a "smoker's cough." Once COPD is established there is little short-term variation, but there is a progressive decline in the longer term (though the course may be punctuated by short-term exacerbations).

Breathlessness may be categorised by the MRC breathlessness scale (Table 4.2). Confusingly, the GOLD guidelines use a modified score, the mMRC. The categories are the same, but use a scale of 0–4 rather than 1–5.

Other clinical factors are determined largely by co-morbidity, but a key factor is that limitation of activity (in terms of ordinary daily activity as opposed to exercise) is curtailed even in Stage 1 disease. This reduction is independently linked to mortality. COPD also leads to a marked reduction in health-related quality of life, which is rather loosely though statistically significantly linked to disease severity as scored by FEV_1.

In addition to smoking, a history of workplace exposure to dust and chemicals, for instance in the mining and steel industries, may make a significant contribution [10].

Table 4.2 MRC and mMRC breathlessness scales

Scale Score	Scale Score	Description
MRC 1	mMRC 0	Excess breathlessness on marked exertion
MRC 2	mMRC 1	Breathlessness on hills
MRC 3	mMRC 2	Breathlessness limiting speed or necessitating stopping on the flat
MRC 4	mMRC 3	Exercise limited to 100–200 m on the flat
MRC 5	mMRC 4	Housebound or breathlessness on activities of daily living

Exacerbations

According to NICE, "an exacerbation is a sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication" [1]. Whilst clinically what this means may be apparent on a day-to-day basis, the definition is imprecise; the change is a subjective difference from baseline. Further, a circular argument ensues if deciding whether an exacerbation requires treatment when the requirement for treatment is within the definition. Additionally, severity has traditionally been judged on criteria including the necessity for hospital admission, but with changing medical practice this alters with time, and is contingent on social as well as pathological factors. In order to define exacerbations more objectively, diaries such as ExactPro® have been developed. These have made it clear that in addition to traditionally recognised clear-cut exacerbations, there are frequent self-terminating milder exacerbations, often not reported to healthcare professionals, and that these have an adverse overall impact on health-related quality of life.

The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort hoped to identify predictive factors for exacerbation, but was somewhat disappointing. What it did establish was the "exacerbator phenotype." Whilst exacerbations became more frequent with increasing disease severity as judged by FEV_1, even in mild disease, exacerbations were found. Importantly, those who exacerbated in 1 year were likely to exacerbate the

next and *vice versa*. One of the few other predictors of exacerbations was the presence of gastro-oesophageal reflux [9].

Exacerbations may be caused by a variety of common respiratory viruses, by bacteria (particularly *Haemophilus influenza*, and also Moraxella and pneumococci, though occasionally Pseudomonas and other opportunistic pathogens are implicated), and by environmental triggers such as particulates and oxides of nitrogen and sulphur. Much of the economic burden of COPD is due to the cost of treating exacerbations. For patients, they cause not only increased symptoms and decreased quality of life, but also have an independent negative prognostic impact [11]. Indeed, for patients admitted to hospital with an acute exacerbation of COPD, all cause of mortality is higher than for those admitted with an acute myocardial infarction. Although median time to recovery of symptoms is 7 days, peak flow fails to recover to baseline in 7% of subjects at 91 days. This prolonged perturbation is also reflected in mortality figures, with excess mortality persisting after discharge in those admitted to hospital for an exacerbation. Formerly it was thought that exacerbations were "bad luck" events occurring largely by chance, but it has become clear they are in fact clustered; one exacerbation is often followed by another, with further long-term impact.

Co-morbidity

The fact that COPD presents in older smokers means it is no surprise to find evidence of other smoking-related diseases such as heart disease and cancer. However, it has become apparent that a number of conditions are present in patients with COPD above and beyond that expected when allowing for these shared risk factors. These diseases include ischaemic heart disease and heart failure, osteoporosis, renal disease, and diabetes. Two possible mechanisms have been suggested to account for this. Firstly, COPD is associated with uncontrolled inflammation within the lung and it is suggested that this "spills over" from the lung, causing chronic systemic exposure to inflammatory mediators with passive bystander damage. Perhaps more likely is that there is a shared genetic predisposition to chronic and excessive inflammation at different sites. Only one-quarter to one-third of smokers develop COPD, suggesting a genetic background leading to "sensitive lungs" in which excessive and uncontrolled inflammation occur in response to the noxious stimulus of cigarette smoke. In this model an individual's genetic background will predispose to excess inflammatory response not only to cigarette smoke in the lungs, but also to lipid deposition in inflammatory atherosclerotic plaques with accelerated coronary artery disease, and so on through the body. The genetic background is highlighted in alpha-1 antitrypsin deficiency. Smokers who are homozygous for this autosomal recessive condition develop early emphysema and indeed, non-smoking subjects may develop emphysema. However, usually the predisposition is polygenetic, and efforts to characterise an individual's genetic risk have yet to be successful.

In assessing and treating individuals with COPD it is important to proactively seek co-morbidity and to treat it in its own right. This may cause important diagnostic challenges; for example the patient with ischaemic heart disease may have breathlessness and chest tightness, but both are common in COPD. Indeed, breathlessness is a cardinal feature of COPD, but exertional discomfort is common too, due to musculoskeletal pain from a hyperexpanded rib cage working at mechanical disadvantage. This is usually not absolutely exercise limiting, and lacks the characteristic radiation of cardiac pain, but tends to persist much longer after exercise (15–60 min). However, the distinction may be challenging clinically. The importance of assessing co-morbidity is emphasised by the TORCH study [12]. This failed to conclusively demonstrate a prognostic benefit from treatment with an inhaled steroid/LABA combination but did critically assess the cause of death in a large cohort of

subjects with an FEV_1 less than half predicted during 3 years of follow-up. Here, only about a third of deaths were due to respiratory failure, with a similar number due to cardiac disease, and about a fifth due to cancers.

There are a number of particularly important extra-pulmonary complications. Whilst inactivity may promote obesity, a more common problem is weight loss, and in particular loss of fat-free mass. Best prognosis is found in those slightly overweight (BMI 25–30), with marked fall with a BMI lower than 20, which is dramatic with a BMI under 15. Recent weight loss is particularly important, whilst a loss of weight during an admission is a predictor of early re-admission.

Whilst in early COPD patients are normoxic, in more severe disease, chronic hypoxia may arise with its own complications. Respiratory failure is defined as a PaO_2 of <8 kPa on air, and is divided into type 1 respiratory failure in which the PaCO2 is normal or low, and type 2 with a high PaCO2.

Respiratory failure (particularly type 2) may give rise to *cor pulmonale* or "right-sided heart failure." Here there is fluid retention with oedema, ascites, and pleural effusions, and an elevated pulmonary artery pressure. Though referred to as "heart failure" the cardiac output is in fact well preserved unless there is co existent left ventricular systolic dysfunction. Although the pulmonary artery pressure is modestly elevated, it rarely exceeds systolic pressures greater than 40–50 mmHg. On the occasions it is substantially more than this, then the prognosis is poor.

Depression and anxiety are common accompaniments of COPD. Whilst it may appear no surprise that those with unpleasant symptoms and activity limitation develop these symptoms, subjects with high anxiety and depression levels have increased symptoms and decreased activity compared to others with similar physical disease, are less concordant with medications, and participate less well in pulmonary rehabilitation and self-management plans. Depression and anxiety are independently associated with poor prognosis.

Epidemiology and Natural History

The global burden of COPD is discussed in the GOLD guidelines, which note self-reported COPD (i.e. people report they have been given this diagnosis) in around 6% of the population in most countries. However, as COPD is often not diagnosed, particularly (but not exclusively) in milder cases, this is no doubt an underestimate. Careful studies in some countries (e.g. Montevideo, Uruguay) report an incidence approaching 20%. In 1990 COPD was thought to be the sixth ranked cause of death worldwide, and it is projected to rise to third with better control of other diseases alongside the expansion of tobacco use in the global south [2].

The definition of COPD used by NICE includes the statement that it is usually progressive [1]. However, recent studies show that it is less predictable [3]. A cohort followed for 3 years revealed that though some showed gradual deterioration (in terms of FEV_1), others deteriorated rapidly, whilst others remained stable or even improved. However, it has not proved possible to differentiate these groups prospectively. Likewise, as discussed earlier, there is a frequent exacerbator phenotype which is difficult to segregate other than by exacerbation history. Whilst in population terms mortality is high, individual survival may be prolonged, even with severe disease. In the TORCH study designed to look at the effect of treatment on mortality, the subjects had, on average, an FEV_1 of under a half predicted and yet 3-year survival was 85% [12]. In our own unpublished audit of 450 subjects commenced on long-term oxygen therapy for severe COPD with respiratory failure, median survival was about 3.5 years, with 15–20% showing prolonged survival, which is of the same order as many cancers treated with radical intent.

Examination

The cardinal feature of COPD is hyperexpansion of the chest, with an increase antero-posterior dimension apparent as a barrel-shaped chest. The

hyoid cartilage is closer to the sternal notch and the area of hepatic dullness may be displaced downwards. The area of cardiac dullness may be diminished. The chest is hyper-resonant, and on auscultation there may be some expiratory wheezes. The term "poor air entry" should be avoided; breath sounds are often quiet, but this may reflect obesity or complications such as pneumothorax.

Hands may show signs of tar staining. Clubbing is not a feature of COPD and should prompt a search for neoplasia. There may be tachypnoea, tachycardia, and signs of CO_2 retention (a coarse flap and altered consciousness). *Cor pulmonale* and pulmonary hypertension may result in a raised JVP, peripheral oedema (and possibly ascites and/or pleural effusion), a right ventricular heave, and a loud P2 on cardiac auscultation. Cardiac signs may be masked by hyperexpanded lung interposed between the heart and the chest wall.

Pathology and Pathogenesis

As noted, COPD is an imprecise term for a collection of conditions, rather than being a unique disease. As such, its pathological appearance is varied [13].

Emphysema relates to destruction of lung parenchyma; the alveoli and respiratory bronchioles in the commoner centrilobular pattern, or more widespread in panacinar emphysema. Confluent areas of destruction may cause macroscopic bullae.

Bronchitis is characterised by submucosal bronchial gland enlargement and goblet cell metaplasia, with mucus hypersecretion. Bronchial glands are inflamed. There is airway epithelial squamous metaplasia, ciliary dysfunction, and hypertrophy of smooth muscle and connective tissue.

The involvement of the smaller airways (<2 mm) is crucial. They are involved early and represent the major site of airflow obstruction, with peribronchial fibrosis and airway narrowing and obliteration. There is inflammation with exudates, goblet cell proliferation, and squamous metaplasia.

The pulmonary vasculature exhibits intimal thickening and endothelial destruction, with later hypertrophy of vascular smooth muscle and collagen deposition, with progressive obliteration of the capillary bed.

Inflammatory changes are found in all these areas. The role of neutrophils has been emphasised mechanistically. In alpha-1-antitrypsin deficiency, neutrophil proteases are not opposed, with resultant tissue destruction and emphysema. However, analogous imbalances are usually difficult to demonstrate in COPD without such specific deficiency. Oxidant damage is important too, both directly and indirectly by modification of proteases and anti-proteases, the complex balance being crucial.

Traditionally, as well as the importance of neutrophils, the controlling role of macrophages and CD8 lymphocytes have been emphasised. This is contrasted with the eosinophilic inflammation and CD4 positive lymphocytes in asthma. However, there is increasing recognition that this is an oversimplification, and a subset of those with COPD may have eosinophilic inflammation too.

Investigations

Pulmonary Function Tests

Spirometry is central to the diagnosis of COPD. NICE [1] and GOLD [2] guidelines characterise airflow obstruction as being an essential component of the disease, requiring the FEV_1/VC post bronchodilator ratio to be <0.7. However, this ratio is age-dependent and, in terms of symptoms, may overdiagnose the elderly and underdiagnose younger subjects. FEV_1 is also used to classify disease. In each case obstruction must be demonstrated. If the FEV_1 is >80% (with symptoms of disease) this is mild (stage 1). In stage 2 (moderate) it is 50–79% predicted, stage 3 (severe) 30–49%, and severe 29% or less. Classically acute reversibility testing may help

differentiate COPD from asthma, with a threshold of a 400 ml improvement in FEV_1 taken as suggestive of asthma. However, there is no sharp cut-off in the degree of FEV_1 change between the two diseases, and reversibility may vary when tested on different days. A number of screening tests such as FEV_6 are available, but should always be backed up by definitive spirometry. Mid-expiratory flows may be affected early in disease, but measurements are poorly reproducible. Oscillometry and multiple-breath gas washout techniques are appealing, as they may selectively measure small airways disease thought to be important in early COPD, but are more complex and not widely used in routine clinical practice.

Fractional expired nitric oxide (FeNO) may help to demonstrate eosinophilic inflammation, but its utility is limited in active smokers.

Alveolar destruction and vascular changes result in poor $V/\dot{Q}$ matching, resulting in a low transfer factor and transfer coefficient (TL_{co} and K_{co}), particularly in emphysematous disease. Hyperexpansion is demonstrated by a large TLC, and gas trapping by a raised RV and RV/TLC. Normally tidal inspiratory and expiratory flow are considerably submaximal and occur at a relaxed lung volume.

With exercise, flow is easily increased, allowing both greater respiratory rate and tidal flow. In COPD there is loss of lung elasticity. Though the increase in intrathoracic pressure occurring during expiration tends to collapse the airways, the lung elasticity splints the airways open. The loss of elasticity in COPD means there is increased airways collapse and this may become flow-limiting at a given lung volume. Increased flow can only be obtained by moving up the flow volume curve to higher volumes, which increases work of breathing and is uncomfortable: a feature known as dynamic hyperexpansion [14]. Complex methodologies may be used in research contexts to study this, but most simply hyperexpansion can be tracked by a fall in inspiratory capacity (IC). This fall in IC (and its change with exercise) is one of the best correlates with decreased exercise capacity and symptoms in COPD. However, its measurement is exacting and is not used in routine clinical practice.

Transcutaneous pulse oximetry is a basic part of assessment of patients with COPD, particular during exacerbations. However, it gives no information on pH or $PaCO_2$, so a low reading requires measurement of blood gases. The gold standard is arterial blood gas measurement, though capillary blood gas measurement is less invasive and has increased patient acceptability, so may be preferred in non-critical situations.

Radiology

Plain chest radiographs may show increased lucency in areas of emphysema or bullae, or diaphragms that are low and flattened, hyperexpansion, and a narrow cardiac silhouette. None of these are pathognomonic and depend on technical factors and body habitus. The main utility of plain radiology in COPD is to identify other factors such as lung cancer, pneumonia, pneumothorax, and heart failure.

Computed tomography (CT) demonstrates areas of emphysema as areas with low Hounsfield units. This may be useful in diagnosis and in planning surgical treatment. Complications such as bronchiectasis and lung cancer can be identified.

Lung perfusion scans may be useful in planning either bulla or lung cancer surgery, identifying poorly perfused areas that can be safely sacrificed. Routine magnetic resonance imaging (MRI) produce poor lung images, as they are proton poor. Coils can instead be tuned to inhaled hyperpolarised inert gases, producing images of gas flow within the lungs, but this remains a research technique.

Blood Tests

Full blood counts may demonstrate anaemia as a cause of dyspnoea, or neutrophilia suggesting infection. A raised blood eosinophil count (for example, $\geq 2\%$, or above the upper quartile of the

normal range) of the total leukocyte count may suggest steroid-responsive disease [8].

Alpha-1-antitrypsin levels may be depressed in this inherited disorder. They may be somewhat low in clinically insignificant heterozygous deficiency, or elevated as part of an acute phase response, so suspect levels should be confirmed by genotyping.

Sputum

Sputum tests may be useful in identifying pathogens in exacerbations, particularly if there has been a failure in treatment. They are not necessarily indicated for isolated exacerbations [1]. In stable disease the airways often contain bacteria. These may be regarded as colonising when there are no clinical signs of exacerbation such as sputum purulence and increased dyspnoea. Though such colonisation may be associated with poorer clinical outcomes, attempts to eradicate bacteria may prove futile, and careful clinical judgement is required.

Exercise Tests

Field exercise tests such as the incremental and endurance shuttle walking tests and the 6-minute walk may be useful in quantifying disability. They are relatively time consuming and other tests, such as sit-to-stand tests, are being investigated. Full cardiopulmonary exercise testing will more formally demonstrate exercise limitation and may occasionally be useful for differentiating cardiac and pulmonary causes of dyspnoea.

Quality of Life (QoL) Scores

Though spirometry is the mainstay of COPD diagnosis, the relationship of quality of life (QoL) scores with FEV_1 is poor (though statistically significant). Questionnaires such as the St. George's Respiratory Questionnaire and the Chronic Respiratory Questionnaire are too cumbersome for routine clinical practice. The COPD Assessment Test (CAT) is a simple eight-question, self-fill questionnaire that is more practical and sensitive to change with exacerbations and interventions, and is reproducible. It forms a useful part of routine assessment.

Composite Scores

The recognition that COPD is a multi-component disease poorly described by FEV_1 alone has led to the development of a number of composite scores. The best known of these is the BODE score, which gives categorical scores which are then summed for body mass index (B), FEV_1 as a measure of obstruction (O), dyspnoea measured by the mMRC score (D), and 6-min walking distance as a measure of exercise capacity (E) (Table 4.3). In populations BODE score is a better mortality predictor than individual components, but for individuals the confidence intervals are broad. However, the predictive power of a change in BODE score in response to an intervention has not been demonstrated, and the accuracy may vary in different populations. As they are categorical, small clinical changes may produce a large change in BODE score and *vice versa.* Thus the utility of such composite scores for individuals is limited.

Table 4.3 BODE score: composite score for prognostic prediction in COPD

Score	0	1	2	3
FEV_1 (% predicted)	≥65	50–64	36–49	≤35
6 MWD	≥350	250–349	150–249	≤149
mMRC	0–1	2	3	4
BMI	>21	≤21		

BMI Body Mass Index (B—BMI), *FEV_1* FEV_1% predicted (O—Obstruction), *mMRC* modified MRC breathlessness score (D—Dyspnoea), *6 MWD* 6 min walking distance in metres (E—Exercise capacity)
Each component is scored, the result summed and the 4-year survival is given below:
0–2 Points: 80%
3–4 Points: 67%
5–6 Points: 57%
7–10 Points: 18%

Differential Diagnosis

Classically, the main differential diagnosis is from asthma. COPD is regarded as fixed airflow obstruction that is slowly progressive in time with little day-to-day or diurnal variation. It is without an allergic component, and whilst there is exercise limitation, post-exercise symptoms are not a feature. Asthma shows short-term and diurnal variation, including in response to short-term treatment or provocative changes (e.g. mannitol or methacholine). Nocturnal and post-exercise symptoms are characteristic. An allergic component is common. COPD tends to arise in the fifth decade or later in smokers, whilst asthma often arises earlier in life, often without any history of smoking. Whilst these distinctions appear clear cut in many text books and guidelines, in clinical practice there are many grey areas. ACOS (asthma/COPD overlap syndrome) is a term coined to cover such areas, but it is unclear whether this truly identifies a distinct group of patients or better guides clinical management. Pragmatically what matters is a diagnostic classification which will help predict treatment response and prognosis. As discussed in the introduction, the current classification does this poorly, and in the future diagnoses based on endotypes are likely to become more common.

Other causes of dyspnoea must be distinguished. Cardiac disease shares age and smoking as risk factors as well as being a disproportionately common co-morbidity. Orthopnoea may suggest cardiac disease but is often present in COPD. Ankle swelling may be part of *cor pulmonale* rather than left-sided heart disease. Exertional chest pain due to musculoskeletal factors resulting from hyperexpansion in COPD and to angina may be difficult to interpret. Exercise electrocardiograms may be non-diagnostic in the dyspnoeic patient of whatever cause, and radionuclide scans may be necessary to demonstrate ischaemia. Measurement of serum BNP may be useful, but may be elevated in left or right sided heart failure. Echocardiography may be limited by poor acoustic windows. Invasive diagnostic procedures may be required.

Some series suggest thromboembolic disease is particularly common in patients with COPD, and CT pulmonary angiography should be considered in patients with exacerbations failing to respond to treatment, especially in the absence of infective symptoms such as altered sputum.

Lung cancer also shares risk factors with COPD and is common. Haemoptysis or clubbing should prompt a search for neoplasia. Patients with COPD often lose weight. Judging when to investigate this separately is a difficult judgement, but a change in weight trajectory, especially with systemic malaise and anorexia, should be viewed with suspicion.

Patients with chronic sputum production and frequent infections should be investigated for bronchiectasis. Some minor degree of bronchiectasis is exceptionally common in COPD and not necessarily of separate significance, but definite bronchiectasis requires additional attention, including a search for underlying factors such as immune deficiency, aspergillus, atypical mycobacteria, rheumatoid arthritis etc. (see Chap. 11).

Interstitial lung disease is easy to overlook. Classically in obstructive lung disease, the FEV_1 is reduced but the VC is preserved. However, as the RV is often very high, this encroaches on VC, which may be relatively reduced. Further, subjects may be unable to breathe out long enough to reach VC, or the manoeuvre may be incomplete because of cough. Thus, it may be difficult to spot coexistent restriction. Patients with interstitial lung disease may be clubbed, have basal crackles on auscultation, and may have an abnormal chest radiograph, but if there is doubt, then extended lung function tests and computed tomography will be required. Some literature reports combined pulmonary fibrosis and emphysema as an entity. However, radiologically, pathologically, and physiologically, the abnormalities are as would be expected as the sum of each disease. As COPD is extremely common, it would be no surprise were some people with interstitial lung disease to have COPD too, and it is not clear this represents a truly distinct condition.

Treatments

Strategy and Guidelines

Space precludes full discussion of all treatments. This section provides a commentary to provide a framework and to understand the approach to therapy. Available clinical guidelines contain executive summaries which should be consulted in conjunction with this chapter [1, 2].

As lung damage in COPD is permanent and largely irreversible, management of COPD should always consider harm reduction first, with smoking cessation and vaccination. Pulmonary rehabilitation is more efficacious than drug treatment and should receive the highest priority, as should attention to diet, social care, and psychological well-being.

Guidelines contain quite extensive algorithms for the pharmacological treatment of COPD. In general, long-term drugs are used with two aims: to relieve symptoms of dyspnoea (and thus to increase activity and exercise capacity), and to prevent exacerbations. The NICE guidelines utilise a scheme based primarily on FEV_1 to do this. All patients are offered a short-acting bronchodilator. For those with an FEV_1 above 50% predicted, a long-acting bronchodilator is recommended if there are persistent symptoms and/or there are frequent exacerbations. For those with a lower FEV_1, long-acting bronchodilators are recommended for those with persistent dyspnoea despite short-acting bronchodilators. However, if there are frequent exacerbations, a combination long-acting beta-2 agonist and inhaled corticosteroid (LABA/ICS) is recommended. Other drug classes may be added if there is a failure of these additional recommendations.

GOLD guidelines attempt a more nuanced approach. In fact the differences between the two guidelines are often overemphasised, as most patients will receive similar treatment whichever guide is utilised. GOLD seeks to recognise that FEV_1 is not a full descriptor of disease, so stratifies patients into symptoms (using dyspnoea and/or CAT score) and "risk" (using exacerbation history and/or severity of airflow obstruction) (Fig. 4.1). Four groups are thus defined: low symptom/low risk (A), high symptom/low risk (B), low symptom/high risk (C) and high symptom/high risk (D). In practice there are rather few patients in group C, and there isn't a simple progression through groups as disease advances in the individual. The categories are less discriminating for prognosis compared to the classification using airflow obstruction alone, as in classification of disease severity by NICE. Nevertheless, this can provide a relatively simple guide to treatment (see guidelines).

Smoking Cessation

Any discussion of treatment of COPD must commence by addressing smoking. No other treatment has been shown to alter disease progression, so are of subsidiary importance. Smoking status should be checked at all reviews, with psychological and pharmacological support easily available.

Organisation of Care

Self-management

In chronic disease, the volume of the task for health care systems as well as patient advocacy has encouraged self-management strategies. In many cases (such as asthma) there is no doubt about the value of such approaches. It has proved much harder to prove self-management has a helpful impact in COPD, with contradictory evidence from available trials. Brief interventions seem futile; success in initiating self-management seems to require much more complex and prolonged education and support.

Strategies particularly focusing on patients having a reserve supply of steroids and antibiotics to initiate in the event of an exacerbation has become the standard of care. Limited evidence exists on the efficacy of this, showing such provision increases utilisation of steroids and antibiotics but without a decrease in use of health care resources or improvement of quality of life. Such provision needs ongoing active monitoring to ensure treatment is used appropriately.

Supported Discharge and Hospital at Home

Antibiotics, steroids and bronchodilators are easily and conveniently delivered in a domiciliary setting. This has encouraged the development of admissions avoidance/hospital at home/supported discharge services which have demonstrated that around a third of patients traditionally admitted to hospital for an exacerbation can be safely and effectively treated at home with adequate monitoring (though around 10% of these will require re-admission as a result of such monitoring). The ability to manage many patients at home depends as much on social support (the ability to cope with daily living) as strictly medical factors.

Telehealth

In many chronic diseases, the use of Telehealth has produced improvements in health. The evidence in COPD is much less secure. This may be because physiological changes do not necessarily antedate a change in symptoms during an exacerbation. If patients are unwell they know this without the need for technology to tell them. Calculations of cost per QALY suggest prohibitive expense. These calculations are based on older, more complex systems. More recent interest centres on far simpler ways of using technology to support self-management, and prompt and remind subjects of appropriate actions.

Non-pharmacological Treatments

Vaccinations

All patients should receive annual influenza vaccination. They should receive a single vaccination against pneumococci.

Pulmonary Rehabilitation

Pulmonary rehabilitation is secondary only to smoking cessation in treatment of COPD [15]. It is a clearly cost-effective treatment, producing impressive improvements in exercise capacity and quality of life, with a decrease in dyspnoea and decrease in anxiety. Inpatient bed days are reduced in the year after pulmonary rehabilitation. The treatment is based on the premise that a decrease in exercise due to dyspnoea produces physical deconditioning, with a further decrease in exercise capacity, a downward spiral being established. A mix of aerobic and strength training reverses this, with classes taking place as a group for two or more sessions per week over 6–8 weeks. The socializing and re-integration of the group may have additional benefits that are difficult to quantify.

Pulmonary rehabilitation is conventionally considered in all with MRC3 breathlessness or worse, but should be offered to all who consider themselves functionally limited. A repeat course should be considered annually as routine. An acute exacerbation is likely to produce accelerated functional loss, so services should be organised to allow early rehabilitation afterwards.

The main limitation of pulmonary rehabilitation is that only two-thirds of those appropriately offered a course will accept it, with further patients dropping out during the course. Acceptance is promoted by positive presentation of benefits by the referring health care professional. It is reduced by transport and access problems, and by depression (though depression is alleviated in those who attend). There are few contraindications. Recent myocardial infarction and unstable cardiac disease are the most important. Musculoskeletal problems and problems working in groups are relative contraindications.

Pharmacological Treatments, Oxygen and Ventilatory Support

Beta$_2$ Agonists

Beta$_2$ agonists can be conveniently divided into short- (SABA) and long-acting agents (LABA). The former (which include salbutamol and terbutaline) are the workhorses of drug treatment in COPD. They provide rapid onset bronchodilation, relieving breathlessness within a few minutes, with an effect persisting for 4–6 h. However, they have no long-term action in terms of preventing exacerbations or altering natural history of disease. LABAs (including salmeterol, formoterol, indacaterol, olodaterol

and vilanterol) not only produce bronchodilation and relieve breathlessness, but also lead to improvement in overall quality of life and reduce exacerbation frequency. The first two are administered twice per day, the others daily. Salmeterol is a partial agonist with a slow onset of action and a dose-response curve which plateaus early, so it has a less favourable profile. All act via β_2 adrenergic receptors on bronchial smooth muscle cells, leading to a rise in intracellular cyclic AMP by activation of G protein-linked adenylyl cyclase. Vilanterol is only available as a combined product with fluticasone fumarate. NICE guidelines suggest LABAs are used to treat breathlessness that persists despite short-acting agents, or for the prevention of exacerbations in those with an FEV_1 greater than 50% predicted (or for exacerbators with poor lung function in the form of LABA/ICS) [1]. There has been concern about possible adverse effects of LABAs in asthma. They are clearly dangerous in asthma if used instead of ICS, but it remains unproven if there are detrimental effects above and beyond this. However, this concern resulted in vilanterol not being available as monotherapy. LABAs appear in practice to be very safe in COPD but may give tachycardia and tremor, and worsen angina, heart failure, and thyrotoxicosis.

Anticholinergics

Anticholinergics can also be divided into short-acting agents (SAMA) and long-acting agents (LAMA). The former are somewhat slower in onset of action than SABAs and act for 6–8 h. Like SABAs they have no appreciable long-term effects, but have useful short-term bronchodilator actions which relieve breathlessness. As their onset in action is slower than SABAs, they tend to be used regularly rather than on an "as required" basis. They act by blocking muscarinic receptors on bronchial smooth muscle myocytes, reducing the bronchoconstrictor action of the vagus nerve. In the case of the LAMAs, there is some selectivity for the M3 receptor, with less blockade of the pre-ganglionic M1 receptors, leaving negative feedback inhibition intact. All reduce exacerbations and improve indices of quality of life, in addition to producing bronchodilation and relieving breathlessness. Aclidinium is given twice per day, whereas tiotropium (the archetypal class member), glycopyrronium, and umeclidinium are given once daily. NICE guidelines suggest LAMA are used to treat breathlessness that persists despite short-acting agents, or for the prevention of exacerbation in those with an FEV1 greater than 50% predicted (or for exacerbators with poor lung function in whom LABA/ICS has failed to produce control, or in whom ICS cannot be used). NICE guidelines do not suggest a preference for LAMA or LABA, but the former are marginally more efficacious. Generally speaking, these are safe drugs, but trials have usually excluded those with a history of recent onset or unstable cardiac disease. Theoretically drugs could have a detrimental effect in these cases, and a safety notice mandates caution in such cases in the UK. Dual LAMA/LABA bronchodilator inhalers lead to 60–70% more bronchodilatation than either of the monocomponents and have become a popular first-line therapy in COPD.

Steroids

With the appreciation that COPD involves ongoing inflammation, a number of trials of inhaled steroids were carried out to see if their anti-inflammatory action would reduce the rate of progression of lung disease (measured as FEV_1). These were uniformly negative. However, the reputation of inhaled steroids was rescued when the ISOLDE trial demonstrated that though the FEV_1 decline was not altered over time, the rate of decline of quality of life was reduced, and this was linked to a reduction in exacerbation frequency. This trial studied those with an FEV_1 of less than 50% predicted. On this basis, inhaled steroids are recommended by NICE guidelines for those with exacerbations and an FEV_1 of <50% [1]. Subsequent trials, however, have suggested benefit in those with better FEV_1. They appear synergistic with LABA and currently both GOLD and NICE guidelines advocate use of ICS only with LABA and not as sole maintenance therapy [1, 2, 12]. Similar research findings have validated the use of fluticasone/salmeterol,

budesonide/formoterol, beclomethasone/formoterol, and fluticasone/vilanterol.

Whilst showing the efficacy of these drugs, recent trials have also revealed that although overall exacerbation frequency is reduced, there is an excess of pneumonias. These are more common in the elderly, those with severe disease, and those with a past history of pneumonia. Overall these seem mild and not associated with excess mortality (except with fluticasone/vilanterol in a dose higher than that licenced). In view of these concerns, the WISDOM trial took subjects with severe COPD treated with LABA/LAMA/ICS combination and carried out a staged withdrawal of ICS and showed no excess of exacerbations over a year (though a slight and perhaps insignificant decline in FEV_1). This has encouraged a reappraisal of the role of ICS. Recent reanalysis of seminal trials establishing the role of ICS suggest that the benefit of ICS may be confined to those with an eosinophil count of ≥2% of peripheral blood leukocytes at the start of the trial. This is within what is usually regarded as the normal range and represents a significant proportion of COPD patients. Risk of exacerbation and steroid-responsiveness in COPD stratify with blood eosinophil count—those with low eosinophil counts (the majority of those with COPD) seem not to benefit from ICS treatment, whilst the most benefit is seen in those with the highest counts. Whilst there are few prospective interventional trials to support this conclusively, the available evidence is consistent and persuasive, but yet to be recognised in major guidelines. Eosinophilic inflammation and steroid response is traditionally associated with asthma, and this finding is one that lends support for the re-examination of disease categorisation aligned to disease endotypes in COPD.

Theophyllines

Theophyllines are adenosine antagonists and also inhibit phosphodiesterase, leading to an increase in intracellular cyclic AMP. They have fallen into disfavour, due to a high incidence of side effects (headache, nausea, diarrhoea, and dysrhythmias) and many drug interaction via the cytochrome P450 system. Their narrow therapeutic index necessitates monitoring of blood levels, adding to complexity. Histone deacetylase-2 (HDAC2) suppresses inflammatory gene activity but is reduced in smokers and patients with COPD, perhaps preventing corticosteroids from suppressing airway inflammation. *In vitro* theophyllines restore histone deacetylase (HDAC) activity. Clinical trials have failed to demonstrate that this theoretical benefit is useful clinically.

Phosphodiesterase Type 4 (PDE4) Inhibitors

PDE4 inhibitors target the phosphodiesterase in bronchial smooth muscle and inflammatory cells (macrophages and neutrophils) that are relevant to COPD. Their selectivity means they have a better therapeutic window compared to non-selective agents. Trials show they reduce exacerbation frequency, but only in those with chronic sputum production. However, they have no overall beneficial effect on QoL, meaning they have not been approved by NICE in the UK and are unfunded, though available elsewhere in the world. The main side effect is weight loss, though this appears to plateau, and fat-free mass is relatively well preserved.

Macrolides and Long-Term Antibiotics

Long-term antibiotics have been used in COPD in an effort to prevent exacerbations. However, little evidence supports this, and it risks development of resistance and it is not recommended. An exception to this is macrolides, where trials of erythromycin and azithromycin have shown clear reductions in exacerbation frequency (though subgroup analysis suggests this is not the case in continued smokers). The anti-inflammatory actions of macrolides are likely to be crucial to this effect, but there is again concern about widespread use leading to resistance. They are not recommended in current guidelines, though are being increasingly used in routine practice. Erythromycin is used at the low dose of 250 mg bd, which limits side effects, but drug interactions (particularly statins) may be an issue in patients requiring drug treatments for multiple comorbidities. In trials azithromycin has mostly been used at 250 mg daily, and this is associated

with a significant incidence of high-frequency hearing loss. Macrolides prolong the QT interval, and caution is advised in patients predisposed by medication or risk factors for dysrhythmias.

Mucolytics

There is conflicting evidence on the use of mucolytics long term to reduce exacerbation frequency. They may provide symptomatic benefit by allowing ease of expectoration of mucus, and a therapeutic trial may be carried out.

Domiciliary Oxygen and Non-invasive Ventilation

Those with established hypoxaemia derive prognostic benefit from prolonged oxygen treatment. UK guidelines specify this should be provided for those with a $PaO_2 < 7.3$ kPa whilst stable and breathing air, on two occasions at least 2 weeks apart [16]. These criteria are relaxed to 8 kPa for those with signs of end organ damage such as cor pulmonale or secondary polycythaemia. Oxygen should be titrated to produce a PaO_2 of 8 kPa, and used for >15 h each day, usually including overnight use. It is provided by the use of an oxygen concentrator, with backup cylinders. On occasion adequate oxygenation cannot be produced without causing an unacceptable rise in pCO_2, and fall in pH. Patients with symptoms of nocturnal hypoventilation and persistent hypercapnia might be considered for a trial of domiciliary nocturnal positive pressure ventilation.

Oxygen therapy has not been shown to relieve breathlessness except in those with significant hypoxaemia. Ambulatory oxygen to abolish hypoxaemia on exercise may reduce symptoms and increase exercise capacity. Oxygen can be provided for those patients with exercise-induced hypoxaemia who improve exercise capacity and/or decrease symptoms in formal exercise tests, though precise thresholds are not specified and, indeed, short-term benefits have not been shown to correlate with longer term QoL benefits.

Opiates and Benzodiazepines

Despite optimisation of all other therapies, some patients may still have distressing breathlessness. Low-dose opiates (10–20 mg of slow-release morphine twice per day) or lorazepam (0.5 mg taken sublingually prn) may relieve the sensation of breathlessness. Whilst in subjects with low (or indeed normal) carbon dioxide levels these are very safe, they are respiratory depressants and some caution is required in those with type 2 respiratory failure. Some risk may be acceptable in those clearly approaching the end of life.

Investigational Treatments

Though there is a long list of treatments in COPD, there is a frustration that even with the best of these, while exacerbations are reduced, they still continue and there has been little if any impact on rate of decline of disease and prognosis. With the understanding of COPD as an inflammatory disease there is an interest in targeting underlying mechanisms, including endotypic targeting, and the use of these earlier in disease to prevent progression before damage is done. These include MAP kinase inhibitors, CXCR2 antagonists, eosinophil and IL-5 antagonists, and others. Whilst some show promise, to date there have been problems with toxicity which have thwarted their utility.

Interventional Treatments

Lung Volume Reduction Surgery (LVRS)

The lung in COPD loses elasticity. Resultant hyperexpansion and gas trapping gives a mechanical mismatch between the chest wall and the lungs. Volume reduction surgery aims to remove particularly damaged areas of the lung which contribute little useful function, with the diaphragm, other respiratory muscles, and the chest wall able to work at better mechanical advantage. The pivotal NETT trial compared optimal medical therapy with surgery (bilateral via sternotomy or thoracoscopy). The primary end point of the trial (prognostic benefit of surgery) was not met. However, exploratory analysis suggested a benefit in those with upper lobe predominant emphysema and poor exercise capacity and prognostic detriment where the opposite conditions pertained. Those with either poor exercise capacity or upper lobe predominant emphysema (but not

both) derived a variable amount of symptomatic benefit.

Applicability of this technique is limited, as only a small subgroup of people with COPD are fit for major surgery. Even in carefully selected subjects there is an acute mortality rate of 2% or 3%, and though groups likely to benefit can be identified, individual success is variable.

Endoscopic Volume Reduction Surgery and Associated Techniques

Endobronchial valves aim to produce the same physiological effects as LVRS but utilising minimally invasive techniques. They are placed endoscopically in bronchi supplying target lung, allowing air to leave but not return, resulting in segmental or lobar collapse. Collateral ventilation within the lung will cause this to fail, and may be predicted if there are incomplete fissures on CT scan, or directly measured by endobronchial catheter pressure/flow measurement using Chartis® (see Fig. 4.2 for research imaging of collateral ventilation). Target areas can be identified using CT to show areas of maximal emphysema, with perfusion scanning showing areas with poor blood supply. Physiologically, those with high TLC and RV are most likely to benefit.

A randomised control trial of treatment versus sham bronchoscopy shows good improvements of lung function and quality of life. However, scrutiny of individual results shows a subgroup little changed by treatment, whilst others gain a substantial improvement. It is unclear how to differentiate these in advance. However, this is a

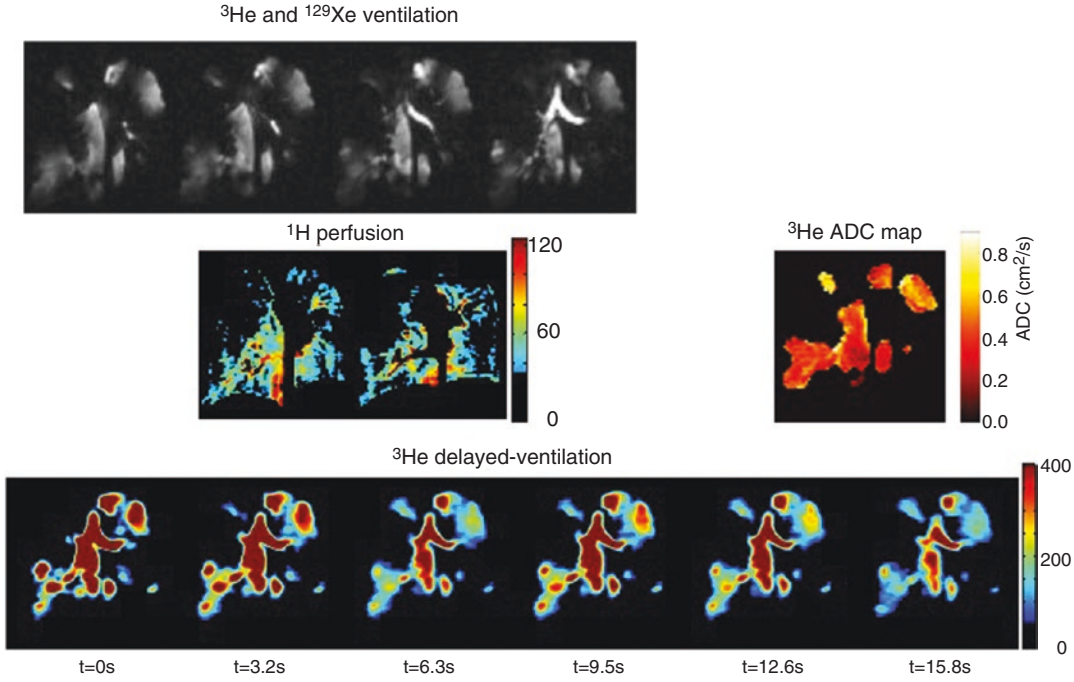

Fig. 4.2 Magnetic resonance lung imaging with demonstration of collateral ventilation (Images used with permission from Lawson RA, Wild J, and Marshall H. Sheffield, UK). *Upper panel*: Images of lung ventilation. ^{3}He or ^{129}Xe are polarised and are imaged by a tuned coil to directly image gas in the lungs. The images show the patchy distribution of ventilation with large areas largely devoid of ventilation in a patient with COPD. *Middle panel*: gadolinium enhanced proton MRI (left), showing variable perfusion of lungs in a patient with COPD. On the right is a map of the apparent diffusion coefficient (ADC). This measures the mean free path of gas molecules and hence relates to alveolar size; that is, to emphysema (though it can only assess areas of lung that are ventilated). *Bottom panel*: MRI images during a breath hold after inhalation of polarised He^{3}. Time of acquisition of successive images is shown below in seconds. Maximum ventilation is reached early in most areas, but is delayed in the right upper zone, representing collateral ventilation

minimally invasive procedure which appears reasonably safe, and valves can, if necessary, be retrieved should problems ensue. The major acute side effect is pneumothorax, though subjects suffering this appear to do well long term. Most clinical trials are short term (less than a year) so long-term safety has yet to be fully established.

Endobronchial coils are also deployed bronchoscopically, acting as splints to open airways and combat lack of elasticity. Potentially, they may complement valves, as they are unaffected by collateral ventilation. As of 2015 the world literature reported about 150 procedures, of which a minority were treated in randomised, controlled trials. Publication of a completed large RCT is awaited.

Lung Transplantation

The utility of transplantation in COPD is limited, as the disease affects older subjects who typically have significant co-morbidity. However, it has a role in younger subjects with isolated lung disease. Historic series suggest only a modest prognostic benefit, but there may be significant quality of life advantage. Selection of appropriate candidates is complicated by the uncertain prognosis in COPD.

Treatment of Exacerbations

Simple exacerbations are treated with an increase in bronchodilators. No increased efficacy has been demonstrated for delivery by nebulisers, but this may be a convenient form to deliver larger doses. A proportion of exacerbations are associated with bacterial infection, which is suggested by the production of purulent sputum and systemic features of infection (fever, malaise, leucocytosis, raised CRP, and procalcitonin). Antibiotics should cover pneumococci, *Haemophilus influenzae*, and Moraxella. The choice should be guided by local policies, and may include doxycycline and co-amoxiclav. Oral steroids are frequently used, though have limited efficacy. Trials suggest they may speed recovery, lessening hospital stay by a day, but without affecting ultimate outcome. There is no benefit from prolonged courses beyond 5–7 days, though if courses have been so frequent as to cause adrenal suppression, they may need to be reduced gradually. Given their wide range of side effects, they should not be considered essential for mild exacerbations. A recent trial suggested only those patients with higher eosinophil counts derived benefit.

As discussed, many exacerbations can be managed in the domiciliary setting, supplemented by home monitoring as needed. The development of hypoxaemia is more complex. Patients with COPD are at risk of CO2 retention, so oxygen can only be safely delivered with the ability to measure blood gases and titrate oxygen appropriately. Usually this can only be delivered in hospital. Initial oxygen should be given to achieve an oxygen saturation of 88–92% until blood gases have been measured [17]. If the pCO2 is normal or low, the target can be revised to 94–98% (unless there are known to be previous episodes of type 2 failure). If the pCO2 is elevated, the lower target should be maintained.

If respiratory acidosis is present after initial treatment despite appropriate oxygen saturation, ventilatory support should be considered. Non-invasive ventilation is potentially life-saving in this situation, emphasising the importance of early hospital referral and correct evaluation of blood gases in the event of hypoxaemia in exacerbations. However, it is also true that this can be a difficult and unpleasant treatment, and may not be appropriate for those clearly approaching the end of life. Sometimes invasive ventilation may be appropriate, though there is a concern about prolonged ventilation and difficult weaning in those with particularly severe disease and significant co-morbidity. Ideally there should be advanced consideration of the appropriate ceiling of intervention involving the patient and family, and the multi-disciplinary clinical team.

Summary

Management of COPD stands at a crossroads. Extensive guidelines should be consulted for current standards of care. However, it is a collection of poorly confined conditions with multiple subtypes. Coming years are likely to lead to increased mechanistic understanding with a need for greater diagnostic clarity. The goal of therapies able to modify disease trajectory may yet be achieved, and diagnostic categorisation allowing more usefully targeted treatment selection is very likely to change clinical practice significantly.

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