Fast Facts:
Chronic Obstructive Pulmonary Disease

William MacNee and Stephen I Rennard
Second edition

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Fast Facts: Chronic Obstructive Pulmonary Disease

Second edition

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Declaration of Independence
This book is as balanced and as practical as we can make it.
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Glossary of abbreviations

BMI: body mass index

BODE index: a measure of disease severity that incorporates body mass index, obstruction, dyspnea and ability to exercise

cAMP: cyclic adenosine monophosphate

COPD: chronic obstructive pulmonary disease

CT: computed tomography

DLco: diffusing capacity in the lung for carbon monoxide (sometimes called TLco in the UK)

ECG: electrocardiography/electrocardiogram

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity (the total volume of air that can be exhaled from a maximum inhalation to a maximum exhalation)

GOLD: Global initiative for chronic Obstructive Lung Disease

HRCT: high-resolution computed tomography

ICU: intensive care unit

IL: interleukin

Kco: carbon monoxide transfer coefficient (DLco/Vₐ)

MRC: Medical Research Council (UK)

NHLBI: National Heart, Lung and Blood Institute (USA)

NIPPV: non-invasive intermittent positive-pressure ventilation

PaCO₂: partial pressure of carbon dioxide in arterial blood

PaO₂: partial pressure of oxygen in arterial blood

PEF: peak expiratory flow

SaO₂: percentage oxygen saturation of arterial blood

SGRQ: St George’s Respiratory Questionnaire

Vₐ: ventilated alveolar volume, or accessible lung volume

Vₜ: tidal volume

VC: vital capacity

WHO: World Health Organization
Introduction

Chronic obstructive pulmonary disease (COPD) has not always elicited sympathetic interest from the medical community. In their groundbreaking monograph on the natural history of COPD, Fletcher and colleagues chose the following quote to emphasize the self-perpetuating attitude that has unfortunately inhibited the understanding and management of COPD.

‘...medicine has come a long way since 1925, when Williams, writing Middle Age and Old Age, could confidently assert: “Chronic bronchitis with its accompanying emphysema is a disease on which a good deal of wholly unmerited sympathy is frequently wasted. It is a disease of the gluttonous, bibulous, otiose and obese and represents a well-deserved nemesis for these unlovely indulgences ... the majority of cases are undoubtedly due to surfeit and self-indulgence.”’

Since the landmark study of Fletcher and Peto, great gains have been made in understanding the pathogenesis, physiology, clinical features and management of COPD. Cigarette smoking, itself now regarded as a disease, is the major risk factor. However, COPD also occurs in non-smokers, and individuals vary greatly in their susceptibility to smoke. Moreover, COPD is a heterogeneous collection of syndromes with overlapping manifestations. This has led to considerable variance in definitions, which has confounded epidemiological and cross-national studies. The Global initiative for chronic Obstructive Lung Disease (GOLD) was recently implemented in order to provide some uniformity. GOLD defines COPD as: ‘a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. The pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles and gases’.

COPD was estimated to be the twelfth leading cause of morbidity and the sixth leading cause of death worldwide in 1990. Of all the major diseases, COPD presents the fastest increasing healthcare burden. By 2030, mortality from COPD is predicted to more than double,
accounting for more than 5.6 million deaths (Table 1). COPD patients, moreover, often make few complaints despite suffering considerable disability. As a result, although COPD can easily be diagnosed, it frequently is not.

The relationship between asthma and COPD has been particularly troublesome. Defining asthma as ‘reversible’ led to the inference that COPD is ‘irreversible’ and, therefore, that there was nothing to ‘reverse’ with treatment. This incorrect belief has served only to exacerbate the underdiagnosis and undertreatment of COPD. Distinguishing between

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<th>Causes of death in 2002 and projected figures for 2030 ($\times 10^3$)</th>
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<td>Number of deaths in 2002</td>
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<tr>
<td>HIV/AIDS</td>
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<td>Diabetes mellitus</td>
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<td>Accidents/unintentional injuries</td>
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<td>Digestive diseases</td>
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<td>Respiratory infections</td>
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<td>Perinatal conditions</td>
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AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
Data from Mathers and Loncar, 2006.
asthma and COPD can be difficult. Both conditions are associated with chronic airway inflammation, although the underlying chronic inflammation is very different in each disease. Both conditions can occur in the same individual and some patients with asthma may progress to COPD, even in the absence of smoking. The clinical problem, however, is not whether a patient has asthma or COPD, but rather whether either asthma or COPD is present, or both.

COPD is associated with a number of comorbidities. While most are common conditions, they are seen more frequently in patients with COPD than would normally be expected. This has led to the concept that COPD has systemic effects, perhaps due to an underlying chronic inflammatory process. Often these comorbidities present major clinical problems in the individual patient for whom the recognition and treatment of COPD is key to management.

COPD is a very expensive disorder. Costs in the USA are estimated to be nearly $40 billion annually; two-thirds of these costs are direct and one-third indirect. Since COPD is significantly underdiagnosed, these estimates are likely to be highly conservative. Most costs associated with COPD are due to exacerbations, particularly those that result in hospitalization. Since exacerbations increase in frequency and require a greater level of care as COPD progresses, most costs are incurred towards the end stage of the disease. General healthcare costs are also increased in COPD patients, emphasizing the multisystem problems faced by this patient group.

Previous guidelines have emphasized treatment for patients who have lost 50–65% of their lung function. Recent guidelines, however, recognize that diagnosis and treatment of COPD at earlier stages can have substantial benefits for the patient. While currently available treatments are unable to cure COPD, they can reduce symptoms, improve lung function and reduce exacerbations, and may decrease the healthcare costs associated with the disease. In addition, treatment may slow the rate of decline in lung function and has demonstrable effects on mortality that approach statistical significance.
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Key references


In COPD, pathological changes occur in the central conducting airways, the peripheral airways, the lung parenchyma and the pulmonary vasculature. Inflammation induced by cigarette smoke underlies most pathological lesions associated with COPD. Inflammation also contributes to recurrent exacerbations of COPD, in which acute inflammation is superimposed on the chronic disease. There is now good evidence that all smokers develop lung inflammation; however, some individuals are more susceptible to the effects of cigarette smoke and are more severely affected. The pathogenesis of COPD in non-smokers has been less studied, but inflammation secondary to air pollution or other substances is likely to play a key role. The extent of the pathological changes in the different lung compartments varies between individuals and results in the clinical and pathophysiological heterogeneity seen in patients with COPD.

Some believe that chronic asthma should be included as part of the spectrum of COPD. Although the clinical and physiological presentation of chronic asthma may be indistinguishable from that of COPD, the pathological changes are distinct from those in most COPD cases due to cigarette smoking. Histological features of COPD in the 15–20% of COPD patients who are non-smokers have not been well studied.

**Chronic bronchitis**

Chronic bronchitis is defined clinically by the American Thoracic Society and the UK Medical Research Council as: ‘the production of sputum on most days for at least 3 months in at least 2 consecutive years’. This chronic hypersecretion of mucus results from changes in the central airways – the trachea, bronchi and bronchioles over 2–4 mm in internal diameter. Mucus is produced by mucus glands, which are present mainly in the larger airways, and by goblet cells, found in the airway epithelium.

In chronic bronchitis, hypertrophy of mucus glands occurs mainly in the larger bronchi and is associated with infiltration of the glands by inflammatory cells (Figure 1.1). In healthy never-smokers, goblet cells
make up 10% of the columnar epithelial cells in the proximal airways, but their numbers decrease in more distal airways and are normally absent in the terminal or respiratory bronchioles. By contrast, in smokers, goblet cells are not only present in increased numbers but also extend more peripherally. Metaplastic or dysplastic changes in the surface epithelium may replace the goblet cells of the normal respiratory epithelium in some smokers and thus may reduce the number of goblet cells in the proximal airways. The clinical significance of these varied anatomic alterations is unknown.

Recent studies using bronchoscopy to obtain lavage and biopsy samples together with examination of spontaneous or induced sputum

Figure 1.1 Pathological changes of the central airways in COPD.
(a) A central bronchus from the lungs of a cigarette smoker with normal function shows small amounts of muscle present in the subepithelium and small epithelial glands. (b) In a patient with chronic bronchitis, the muscle appears as a thick bundle and the bronchial glands are enlarged. (c) At a higher magnification, these glands show evidence of a chronic inflammatory process involving polymorphonuclear leukocytes (arrowhead) and mononuclear cells, including plasma cells (arrow). Reproduced from the Global Initiative for Chronic Obstructive Lung Disease Workshop 2001, Original Report, with the kind permission of Professor James C Hogg, University of British Columbia, Canada.
No features specific for COPD are seen on a plain posterior-anterior chest radiograph. The features usually described are those of severe emphysema. However, no abnormalities may be present, even in patients with very appreciable disability. Recent improvements in imaging techniques, particularly the advent of computed tomography (CT) and, more recently, high-resolution CT (HRCT), have provided more sensitive means of diagnosing emphysema in life.

**Plain chest radiography**
The most reliable radiographic signs of emphysema can be classified by their causes of overinflation, vascular changes and bullae.

**Overinflation** of the lungs results in the following radiographic features:
- a low, flattened diaphragm (Figure 5.1): the diaphragm is abnormally low if the border of the diaphragm in the midclavicular line is at or below the anterior end of the seventh rib; and the diaphragm is flattened if the perpendicular height from a line drawn between the costal and cardiophrenic angles to the border of the diaphragm is less than 1.5 cm
- increased retrosternal airspace, visible on the lateral film at a point 3 cm below the manubrium when the horizontal distance from the posterior surface of the aorta to the sternum exceeds 4.5 cm
- an obtuse costophrenic angle on the posterior-anterior or lateral chest radiograph
- an inferior margin of the retrosternal airspace 3 cm or less from the anterior aspect of the diaphragm.

**Vascular changes** associated with emphysema result from loss of alveolar walls and are shown on the plain chest radiograph by:
- a reduction in the 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 transradiance.

Assessment of the vascular loss in emphysema clearly depends on the quality of the radiograph. A generally increased transradiance may simply be due to overexposure.

The development of right ventricular hypertrophy produces non-specific cardiac enlargement on the plain chest radiograph. Pulmonary hypertension may be suggested, taking measurements from the plain chest radiograph of the width of the right descending pulmonary artery, just below the right hilum, where the borders of the artery are delineated against the air in the lungs laterally and the right main-stem bronchus medially. The upper limit of the normal range of the width of the artery in this area is 16 mm in men and 15 mm in women. This increase in pulmonary artery size is often associated with a rapid diminution in the size of the vessels as they branch into the pulmonary periphery. Although these measurements can be used to detect the presence or absence of pulmonary hypertension, they cannot accurately predict the

Figure 5.1 Plain chest radiographs of generalized emphysema particularly affecting the lower zones. (a) Posterior-anterior radiograph showing a low, flat diaphragm (below the anterior ends of the seventh ribs), obtuse costophrenic angles and reduced vessel markings in lower zones, which are transradiant. (b) Lateral radiograph showing a low, flat and inverted diaphragm and widened retrosternal transradiancy (white arrows) that approaches the diaphragm inferiorly (blue arrows).

- vessel distortion, producing increased branching angles, excess straightening or bowing of vessels
- areas of transradiance.