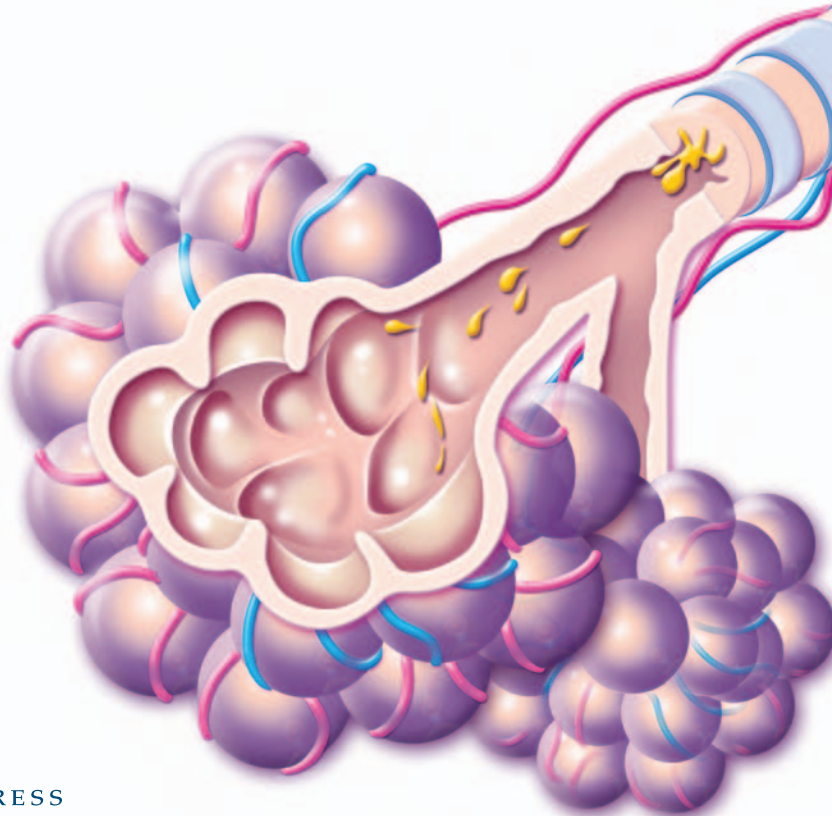


Fast Facts



Fast Facts: Chronic Obstructive Pulmonary Disease

William MacNee and Stephen I Rennard
Second edition





Fast Facts: Chronic Obstructive Pulmonary Disease

Second edition



William MacNee MB CHB MD FRCP

Professor of Respiratory and Environmental Medicine
ELEGI Colt Laboratories
University of Edinburgh Medical School
Edinburgh, UK



Stephen I Rennard MD

Larson Professor of Medicine
Pulmonary and Critical Care Medicine Section
Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska, USA

Declaration of Independence

This book is as balanced and as practical as we can make it.
Ideas for improvement are always welcome: feedback@fastfacts.com



Fast Facts: Chronic Obstructive Pulmonary Disease
First published 2004
Second edition August 2009

Text © 2009 William MacNee, Stephen I Rennard
© 2009 in this edition Health Press Limited
Health Press Limited, Elizabeth House, Queen Street, Abingdon,
Oxford OX14 3LN, UK
Tel: +44 (0)1235 523233
Fax: +44 (0)1235 523238

Book orders can be placed by telephone or via the website.
For regional distributors or to order via the website, please go to:
www.fastfacts.com
For telephone orders, please call +44 (0)1752 202301 (UK and Europe),
1 800 247 6553 (USA, toll free), +1 419 281 1802 (Americas) or
+61 (0)2 9698 7755 (Asia-Pacific).

Fast Facts is a trademark of Health Press Limited.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the express permission of the publisher.

The rights of William MacNee and Stephen I Rennard to be identified as the authors of this work have been asserted in accordance with the Copyright, Designs & Patents Act 1988 Sections 77 and 78.

The publisher and the authors have made every effort to ensure the accuracy of this book, but cannot accept responsibility for any errors or omissions.

For all drugs, please consult the product labeling approved in your country for prescribing information.

Registered names, trademarks, etc. used in this book, even when not marked as such, are not to be considered unprotected by law.

A CIP record for this title is available from the British Library.

ISBN 978-1-905832-54-5

MacNee W (William)
Fast Facts: Chronic Obstructive Pulmonary Disease/
William MacNee, Stephen I Rennard

Typesetting and page layout by Zed, Oxford, UK.
Printed by Latimer Trend & Company Limited, Plymouth, UK.

Text printed on biodegradable and recyclable paper
manufactured using elemental chlorine free (ECF)
wood pulp from well-managed forests.



Glossary of abbreviations	4
Introduction	5
Pathology and pathogenesis	9
Etiology and natural history	20
Clinical features	31
Lung function tests	44
Imaging	69
Smoking cessation	76
Therapy in stable disease	87
Acute exacerbations of COPD	114
Future trends	131
Useful addresses	135
Index	137

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/V_A)

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

V_A: ventilated alveolar volume, or accessible lung volume

V_T: 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

TABLE 1

Causes of death in 2002 and projected figures for 2030 ($\times 10^3$)

	Number of deaths in 2002	Projected number of deaths in 2030	Change (%)
HIV/AIDS	2853	6501	128
Diabetes mellitus	983	2207	124
COPD	2746	5684	107
Cancer	7109	11 485	62
Lung cancer	1242	2242	81
Stomach cancer	850	1389	64
Hypertensive heart disease	908	1338	47
Neuropsychiatric disorders	1109	1627	47
Intentional injuries	1614	2292	42
Stroke	5502	7788	42
Ischemic heart disease	7195	9843	37
Accidents/unintentional injuries	3545	4796	35
Digestive diseases	1964	2325	18
Respiratory infections	4018	2617	-35
Perinatal conditions	2459	1577	-36

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.

Key references

Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;1:1645–8.

Fletcher C, Peto R, Tinker C, Speizer FE. *The Natural History of Chronic Bronchitis and Emphysema: An Eight-Year Study of Early Chronic Obstructive Lung Disease in Working Men in London*. New York: Oxford University Press, 1976:1–272.

Global initiative for chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. NHLBI/WHO Workshop Report. Updated 2008. www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intId=2003 Accessed 12 January 2009.

Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.

Shapiro SD, Snider GL, Rennard SI. Chronic bronchitis and emphysema. In: Mason RJ, Broadus VC, Murray JF, Nadel JA, eds. *Textbook of Respiratory Medicine*. 4th edn. Philadelphia: Elsevier, 2005:1115–67.

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

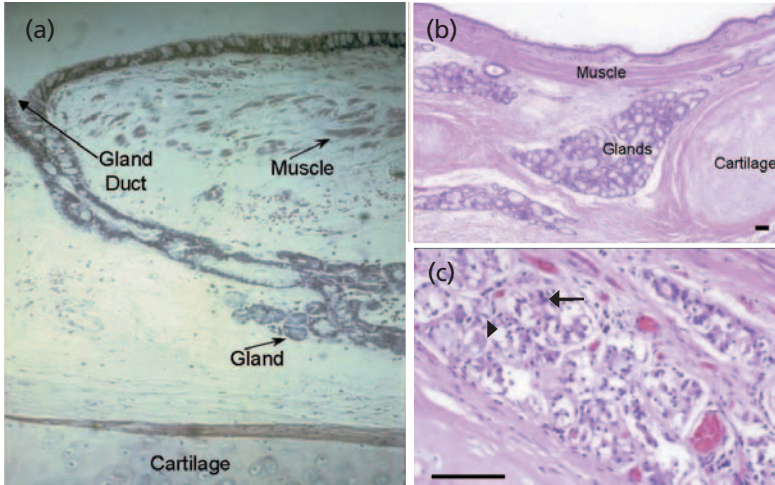


Figure 1.1 Pathological changes of the central airways in COPD. (a) A central bronchus from the lungs of a cigarette smoker with normal function shows small amounts of muscle present in the subepithelium and small epithelial glands. (b) In a patient with chronic bronchitis, the muscle appears as a thick 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.

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

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

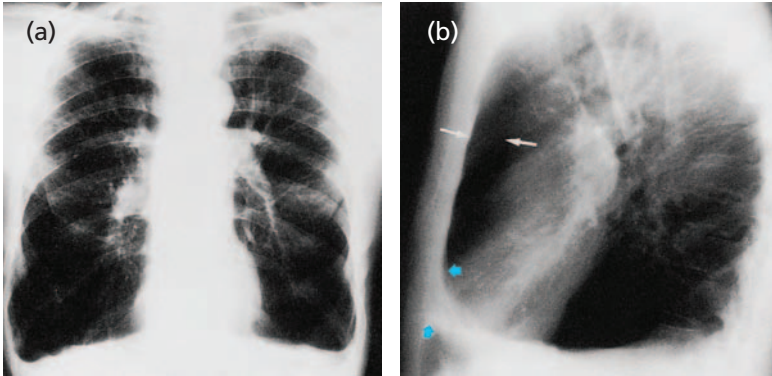


Figure 5.1 Plain chest radiographs of generalized emphysema particularly affecting the lower zones. (a) Posterior-anterior radiograph showing a low, flat diaphragm (below the anterior ends of the seventh ribs), obtuse costophrenic angles and reduced vessel markings in lower zones, which are transradiant. (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 transradiancy.

Assessment of the vascular loss in emphysema clearly depends on the quality of the radiograph. A generally increased transradiancy 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