

SIXTH EDITION

Fishman's PULMONARY DISEASES AND DISORDERS

Michael A. Grippi

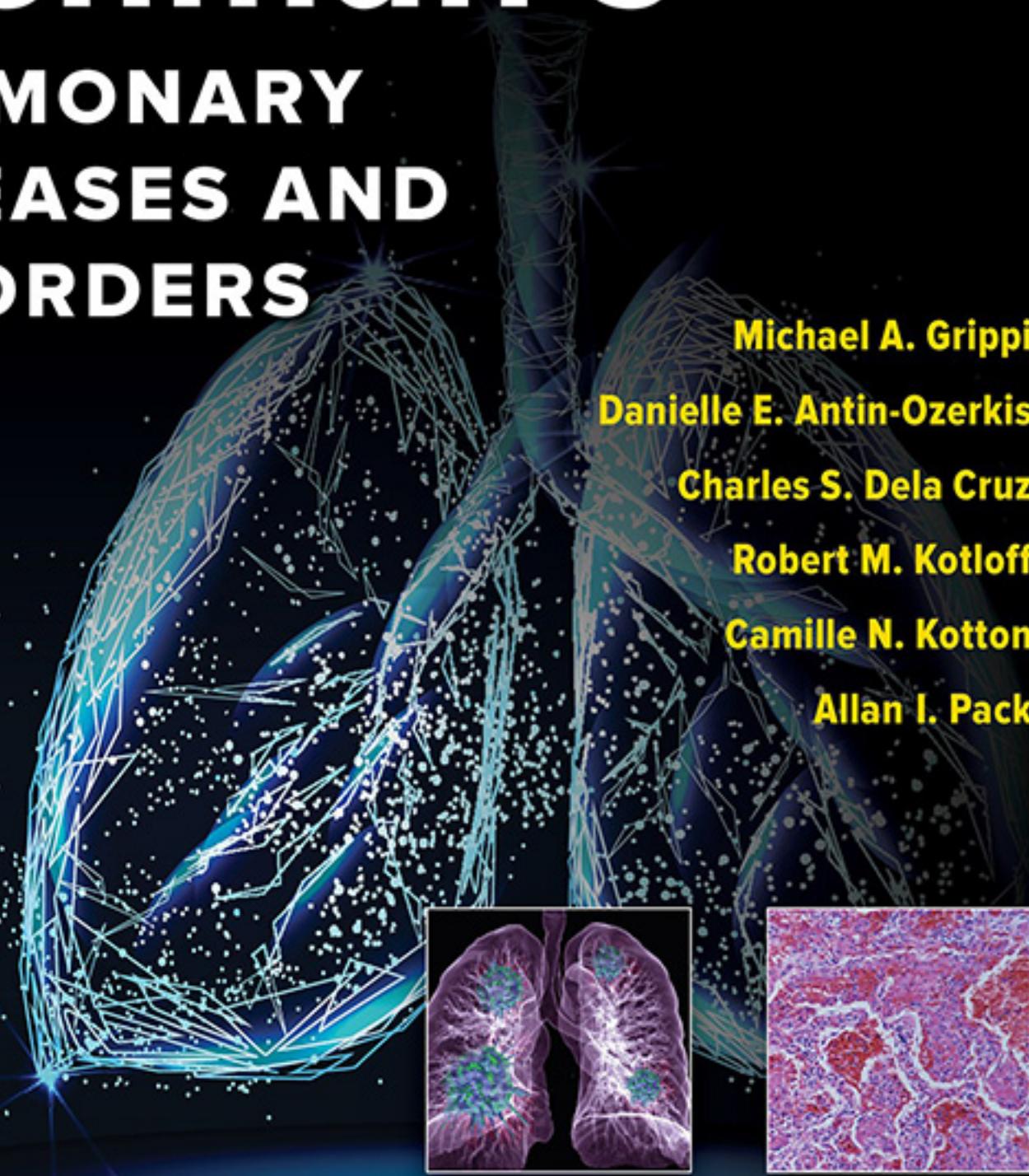
Danielle E. Antin-Ozerkis

Charles S. Dela Cruz

Robert M. Kotloff

Camille N. Kotton

Allan I. Pack



Fishman's Pulmonary Diseases and Disorders

Sixth Edition

Volume 1

EDITOR-IN-CHIEF

Michael A. Grippi, MD

Pulmonary, Allergy, and Critical Care Division
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

EDITORS

Danielle E. Antin-Ozerkis, MD

Medical Director, Yale Center for Interstitial Lung Diseases
Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Yale School of Medicine
New Haven, Connecticut

Camille Nelson Kotton, MD

Associate Professor, Harvard Medical School
Clinical Director, Transplant and Immunocompromised Host
Infectious Diseases
Infectious Diseases Division, Massachusetts General Hospital
Boston, Massachusetts

Charles S. Dela Cruz, MD, PhD

Associate Professor of Medicine
Section of Pulmonary, Critical Care and Sleep Medicine
Associate Professor of Microbial Pathogenesis
Director, Center of Pulmonary Infection Research and Treatment
Yale School of Medicine
New Haven, Connecticut

Allan I. Pack, MBChB, PhD

John Miclot Professor of Medicine
Division of Sleep Medicine
Department of Medicine
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania

Robert M. Kotloff, MD

Craig and Elaine Dobbin/Nancy P. Blumenthal
Professor of Advanced Lung Disease
Perelman School of Medicine at the University of Pennsylvania
Philadelphia, Pennsylvania



New York Chicago San Francisco Lisbon London Madrid Mexico City
Milan New Delhi San Juan Seoul Singapore Sydney Toronto

Copyright © 2023 by McGraw Hill LLC. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-1-26-047406-0
MHID: 1-26-047406-2

The material in this eBook also appears in the print version of this title: ISBN: 978-1-26-047398-8,
MHID: 1-26-047398-8.

eBook conversion by codeMantra
Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw Hill eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

Library of Congress Cataloging-in-Publication Data

Names: Grippi, Michael A., editor.

Title: Fishman's pulmonary diseases and disorders / editor-in-chief, Michael A. Grippi ; co-editors, Danielle E. Antin-Ozerkis, Charles S. Dela Cruz, Robert M. Kotloff, Camille N. Kotton,

Allan I. Pack

Other titles: Pulmonary diseases and disorders

Description: Sixth edition. | New York : McGraw-Hill Education, [2023] | Includes bibliographical references and index. | Summary: "A presentation of pulmonary and critical care medicine with the underlying basic and applied science upon which the clinical material is based. The book includes relevant respiratory biology and underlying cellular and molecular mechanisms, and incorporates of a number of videos designed to complement and, at times, accentuate information contained within the text"— Provided by publisher.

Identifiers: LCCN 2021052087 | ISBN 9781260473988 (hardcover ; set ; alk. paper) | ISBN 9781260474060 (ebook)

Subjects: MESH: Lung Diseases

Classification: LCC RC756 | NLM WF 600 | DDC 616.2/4–dc23/eng/20220510

LC record available at <https://lccn.loc.gov/2021052087>

TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

SECTION 7 Chronic Obstructive Pulmonary Disease

CHAPTER 37

Pathology of Chronic Obstructive Pulmonary Disease: Diagnostic Features and Differential Diagnosis

Joanne L. Wright
Andrew Churg

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a general name for the chronic airflow obstruction that develops most often as a result of chronic tobacco smoking, but also after exposure to biomass fuels and air pollution. The pathology of COPD encompasses a variety of pathologic lesions in the airways, lung parenchyma, and pulmonary vasculature, and these lesions can be correlated, to a greater or lesser degree, with changes in pulmonary function tests and clinical appearances. In general, although the mechanisms involved are complex, airflow obstruction can be attributed largely to a marked increase in airway resistance secondary to a variable mix of structural abnormalities involving all or many of the compartments of the airway. However, in individual cases, it may be difficult to prove associations between physiologic abnormalities and pathologic changes. The Global Initiative on Obstructive Lung Disease (GOLD), revised in 2017,¹ classifies patients with COPD upon a combination of indices of airflow, assessment of symptoms, and exacerbation history; thus far there is only limited integration with pathologic findings.

This chapter presents the pathologic features of COPD and how these findings can be differentiated from other lesions associated with airflow obstruction.

HISTORY OF PATHOLOGIC DESCRIPTIONS OF COPD

The word emphysema is derived from Greek and means “to blow into,” hence “air-containing” or “inflated.” Although “voluminous lungs” and lungs “turgid particularly from air” were described respectively by Bonet in 1679² and Morgagni in 1769,³ the first description of enlarged airspaces in emphysema in the human, together with illustrations, was furnished by Ruysh in 1721,⁴ followed by Matthew Baillie in 1807, who not only clearly recognized and illustrated emphysema, but also pointed out its essentially destructive character.^{5,6}

Laennec,⁷ writing in the early 1800s, made a number of seminal contributions to the basic descriptions of pathologic changes in COPD. He was the first to make a clear-cut distinction between interstitial emphysema and emphysema proper, and related the enlarged airspaces to the clinical syndrome of emphysema. He also recognized that air trapping and increased collateral ventilation were features of emphysematous lungs, and that the peripheral airways

were the primary site of obstruction in emphysema. Furthermore, he noted that airspaces enlarged with increasing age, and he distinguished these changes from emphysema. He was the first to describe an association of emphysema with chronic bronchitis and to clearly describe the pathology of bronchiectasis.

Little of major importance was added to the gross descriptive morphology of emphysema for almost the next 150 years. The foundation of modern knowledge of the pathologic anatomy of pulmonary emphysema was laid by J. Gough in 1952⁸ when he described centrilobular emphysema and distinguished it from panlobular emphysema. The paper section technique developed by Gough and Wentworth⁹ was largely responsible for this advance, as it made examinations of sections of entire inflated lungs possible and simple (Fig. 37-1). A comprehensive microscopic description of emphysema was then provided by McLean,^{10,11} who demonstrated the relationship of destruction to inflammatory alterations of the bronchioles and discussed the observed alterations of the vasculature.

LESIONS OF THE LUNG PARENCHYMA IN COPD: EMPHYSEMA

A major problem in describing the pathologic features of emphysema has been the lack of a generally accepted and easy to apply definition. In 1959, a Ciba Guest Symposium defined emphysema in anatomic terms as “a condition of the lung characterized by increase beyond the normal of airspaces, distal to the terminal bronchiole, either from dilatation or from destruction of their walls.”¹² Subsequent definitions differed in that destruction of respiratory tissue became a requirement:^{13–15} “Emphysema is a condition of the lung characterized by abnormal, permanent enlargement of the

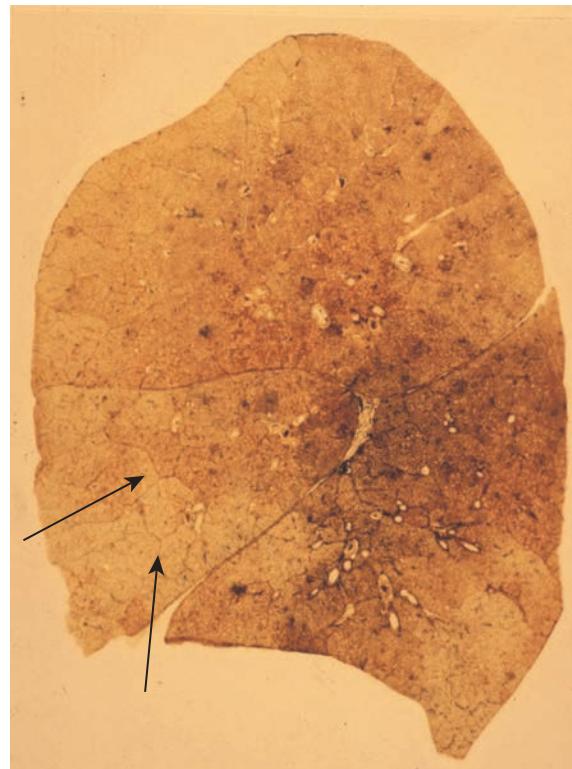


Figure 37-1 Gough sagittal section. Paper mount. Normal lung.

airspaces distal to the terminal bronchiole, accompanied by destruction of their walls.” This requirement separates emphysema from enlargement of airspaces unaccompanied by destruction, the latter now being termed “overinflation.”

Destruction has been similarly difficult to define in an unambiguous way. A committee of the National Institutes of Health¹⁶ proposed that destruction was present when “there was nonuniformity in the pattern of respiratory airspace enlargement so that the orderly appearance of the acinus and its components is disturbed and may be lost.” They recognized that emphysema was a subset of airspace enlargement defined as “an increase in airspace size as compared with the airspace of normal lungs. The term applies to all varieties of airspace enlargement distal to the terminal bronchioles, whether occurring with or without fibrosis or destruction.” While these definitions, when strictly applied, would eliminate airspace enlargement due to overinflation or failure of septation, they would not eliminate airspace enlargement due to reorganization of the airspaces, such as is found in honeycomb lung. This may be part of the confusion when combined emphysema and fibrosis is considered (see below).

CLASSIFICATION OF EMPHYSEMA

Not only is emphysema defined in terms of lung structure, it is also classified in similar terms; therefore, several anatomic definitions are important. The part of the lung involved in emphysema is the acinus, which is defined as the unit of lung structure distal to the terminal bronchiole (final generation membranous bronchiole) and that consists of three orders of respiratory bronchioles: a single order of alveolar ducts, followed by the alveolar sacs, and finally the alveoli. Alveolar ducts are entirely alveolated and characteristically contain smooth muscle around the mouths of their alveoli. While the walls of alveolar sacs are also formed entirely by alveoli, muscle is absent. Alveolar pores of Kohn (also known as vents, stomata, or fenestrae) are normal components of adult alveoli, responsible for collateral ventilation. However, they may also be an initial site of destruction in the development of emphysema, particularly centriacinar emphysema.

The acinus is a three-dimensional anatomic structure, but it cannot be easily identified by gross examination. What can be seen instead on the surface of lung slices is the secondary lobule of Miller, defined as the tissue bounded on four sides by interlobular septa or pleura (Fig. 37-1). Lobules vary tremendously in size but are generally 2 to 4 cm on a side and contain between three to five acini. The terminal bronchiole and subtending respiratory bronchioles tend to be situated in the center of the lobule. For this reason, “centrilobular” emphysema (CLE) and “panlobular” emphysema (PLE) are reasonable and widely used approximations for the more accurate “centriacinar” and “panacinar” emphysema (see below).

The ways in which the acini are involved determine the classification of emphysema. There are four recognized patterns (Fig. 37-2). The acinus (and lobule) may be more or less uniformly involved; this is panacinar (panlobular) emphysema. The proximal portion of the acinus (center of the lobule) may be dominantly involved; the best term for this lesion is proximal acinar emphysema, although the usual term is centrilobular or centriacinar emphysema. Alternately, the proximal portion of the acinus may be normal,

and the distal part (alveolar sacs and ducts) may be dominantly involved. This is distal acinar emphysema, more commonly referred to as paraseptal emphysema since the lesion is accentuated along lobular septa where the peripheral parts of the acini lie. Finally, the acinus may be irregularly involved, producing irregular emphysema or paracapacitrial emphysema, so called because it is usually associated with obvious adjacent scarring.

MORPHOLOGY OF EMPHYSEMA

The morphologies of the principal types of emphysema are discussed below.

■ Centrilobular Emphysema

This destructive lesion of the respiratory bronchioles has a number of characteristic features on gross examination of the lung. In the *classic* lesion, the enlarged, destroyed respiratory bronchioles coalesce in series and in parallel to produce sharply demarcated emphysematous spaces, separated from the acinar periphery (the lobular septa) by intact alveolar ducts and sacs of normal size. The walls of the emphysematous spaces and adjacent tissue characteristically contain variable amounts of black pigment.

The lesions vary qualitatively as well as quantitatively even within the same lung. There is striking irregularity of involvement of lobules, and even within the same lobule.^{17,18} The lesions are usually more common and become more severe in the upper than in the lower zones of the lung (Figs. 37-3A and 37-4A, B).^{19–24} Most affected are the upper lobe, particularly the posterior and apical segments, and the superior segment of the lower lobe. In cases of severe CLE, the destruction proceeds toward the periphery of the lobule, and the distinction between CLE and PLE becomes blurred.

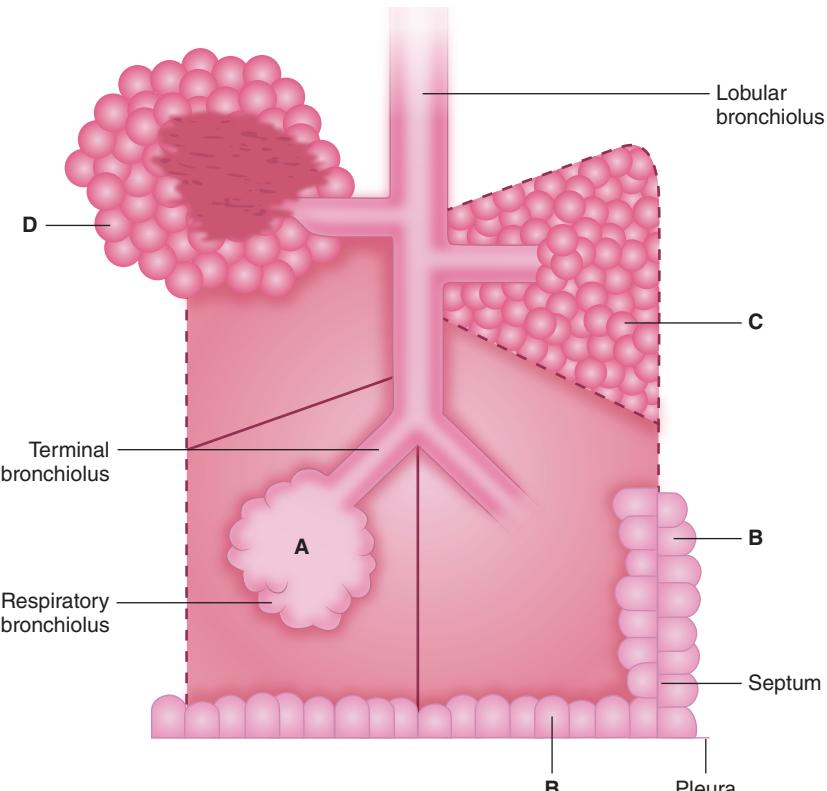


Figure 37-2 Anatomic varieties of emphysema. **A.** Centriacinar (centrilobular). **B.** Paraseptal (distal acinar). **C.** Panacinar (panlobular). **D.** Irregular (scar). The dashed lines mark the edge of the acinus. Only centriacinar and panacinar emphysema are commonly observed in COPD, although paraseptal emphysema often can be found in focal areas in lungs with centriacinar emphysema.

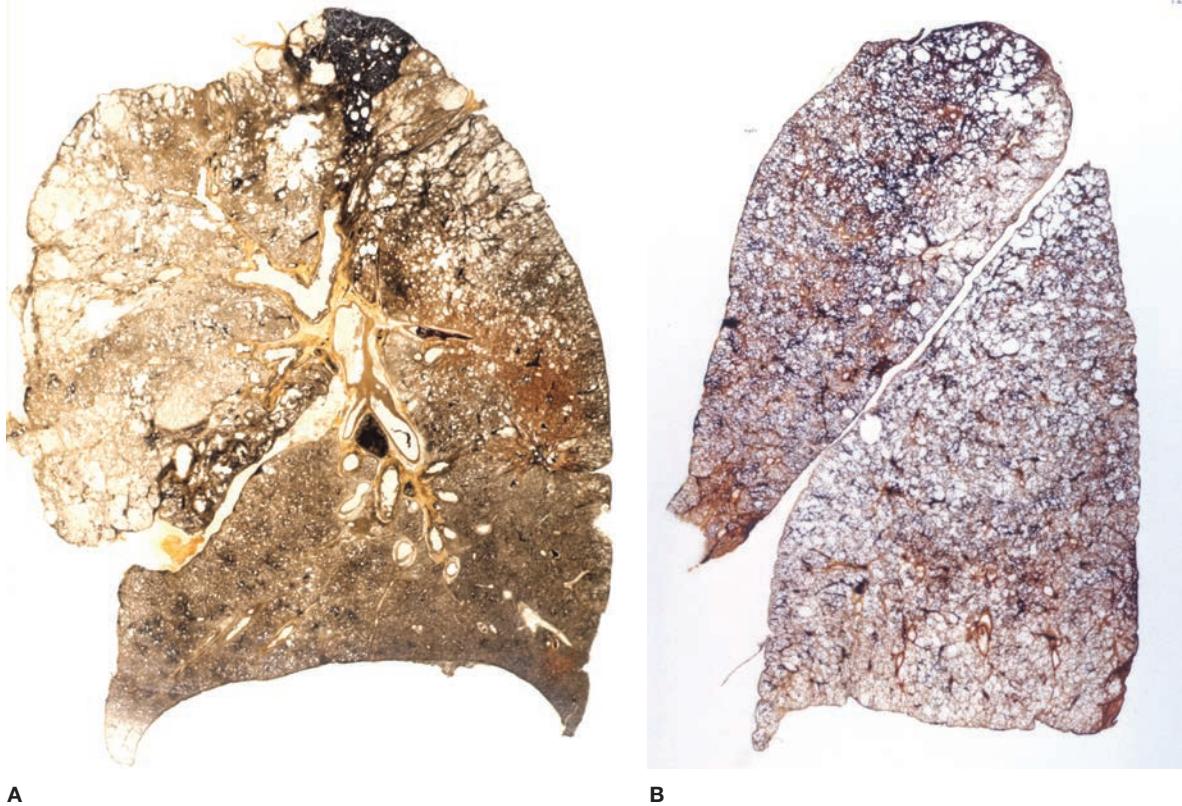


Figure 37-3 Pathologic subtypes of emphysema. **A.** Predominantly centriacinar emphysema. Emphysema is more severe in upper lobes. **B.** Predominant panacinar emphysema. Emphysema is more severe in the lower lobes.

In CLE, alveolar pores are abnormal in size and shape, and occasionally contain epithelial debris and macrophages. Although there are numerous pores of variable size in the emphysematous areas,²⁵ there are also increased numbers of pores in the grossly normal areas, and accentuation of these changes in the center of the lobule.²⁶ Thus, it appears that in CLE the pores of Kohn are possibly the initial site of destruction.

There is increased cellularity in the alveolar walls of cigarette smokers,²⁷ and when this has been quantified, the parenchyma in severe emphysema has increased numbers of neutrophils, macrophages, eosinophils, and both CD4 and CD8 T lymphocytes.²⁸ There is also a significant inflammatory cell infiltrate in the airspaces in severe emphysema, with the same cell types increased.²⁸ Although not readily apparent grossly or on standard histologic stains, use of histochemical stains or biochemical analysis demonstrates that collagen is increased in both centrilobular and panlobular emphysema.^{29–31}

■ Panlobular Emphysema

The gross recognition of mild panlobular emphysema can be very difficult. The normal lung has a very characteristic appearance when seen through a dissecting microscope: The multifaceted alveoli form a contrast to the larger, cylindrical conducting structures that are alveolar ducts and respiratory bronchioles. In panlobular emphysema, the distinction between alveolar ducts and alveoli becomes lost as alveoli lose their sharp angles, enlarge, and then lose their contrast in size and shape with the ducts, resulting in simplification of the lung architecture, with formation of small box-like structures. As the process worsens, the architectural derangement becomes more obvious, with progressive effacement and loss of the orderly arrangement of the lung until little remains other than the supporting framework of vessels, septa, and bronchi. The best way to see

panlobular emphysema grossly is to examine lung slices immersed in a water or fixative bath and then immediately after removal from the bath. The immersed specimen shows enlarged airspaces and, when the slices are lifted from the bath, panlobular emphysema can be suspected because the lung parenchyma “falls away” from the supporting structures which then protrude slightly above the parenchyma. In contrast to centrilobular emphysema, panlobular emphysema is usually worse in the lower lobes (Fig. 37-3B).

Histologic examination is a sensitive method of recognizing panlobular emphysema. The pattern is again one of simplification with diminishing contrast between alveoli and alveolar ducts (Fig. 37-4C, D). Despite the greater extent of tissue destruction, in panlobular emphysema the pores of Kohn are more uniform and inconspicuous than those found in centrilobular emphysema.³²

Panlobular emphysema is the characteristic lung lesion seen in α_1 -antitrypsin deficiency,³³ but may also occur as a consequence of permanent obliteration of airways (obliterative bronchiolitis, constrictive bronchiolitis). Most often, obliteration of airways results in collapse of the distal lung parenchyma and dilatation of the bronchi proximal to the obliterated airways. This is the sequence of events in postinfective bronchiectasis. In some instances, however, the lung parenchyma does not collapse, but remains fully expanded or becomes emphysematous. The parenchymal sequel to bronchial and bronchiolar obliteration depends on the extent of the obliteration and the amount of collateral ventilation between adjacent airspaces distal to unobstructed airways. If collateral ventilation is present, then the units distal to the obliterated airways will remain expanded by virtue of the air reaching them by collateral ventilation, producing overexpansion and destruction of lung parenchyma beyond the obliterated airways. The terms *Swyer-James* or *MacLeod syndrome* are applied when this process affects most of one lung, or lobe of lung, but spares the remainder.

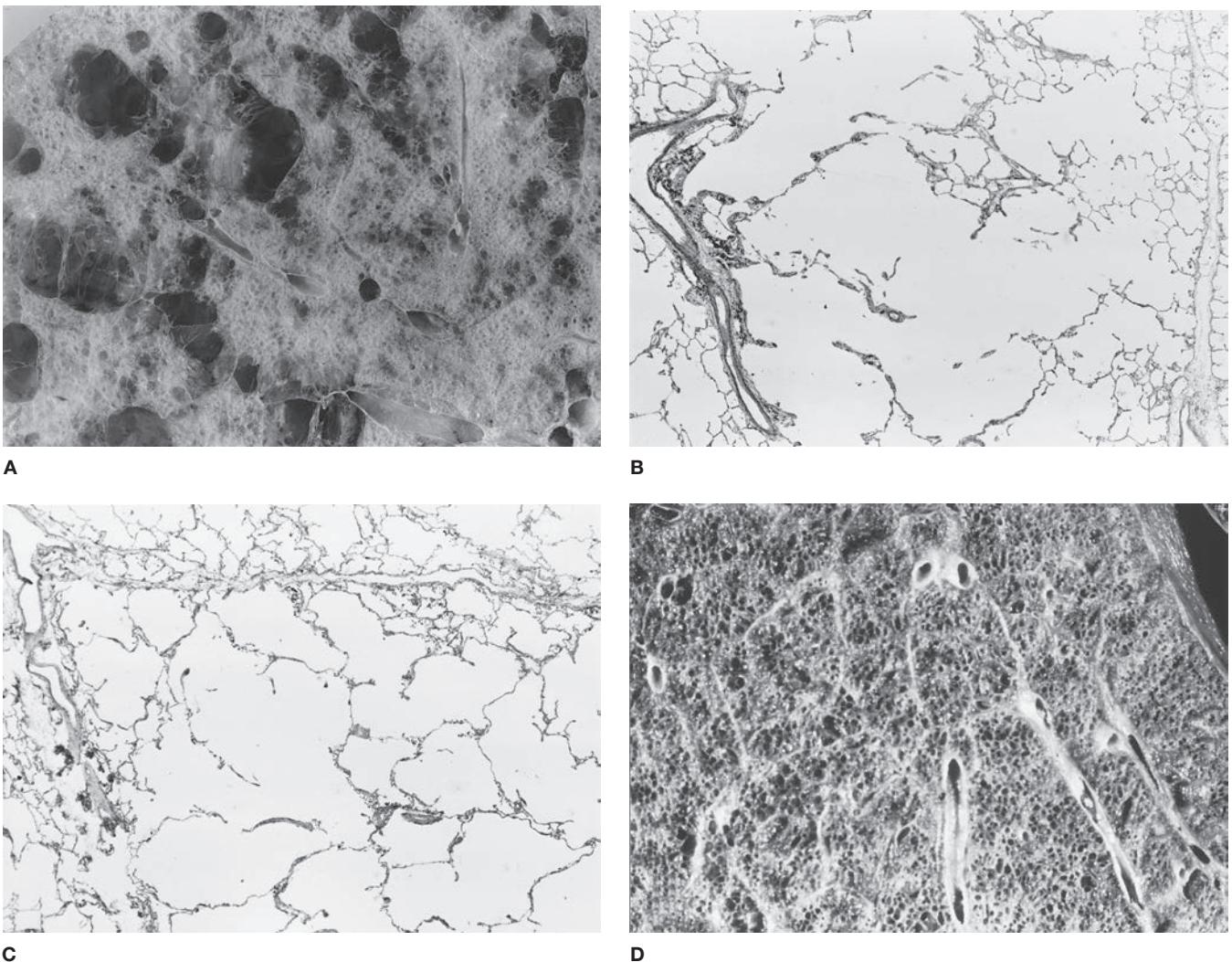


Figure 37-4 **A, B.** Gross and histologic sections illustrating centriacinar; and **(C, D)** panacinar emphysema. **A.** Cut surface from a lung with centriacinar emphysema showing holes in the center of lobules surrounded by relatively normal parenchyma. The severity varies among lobules. **B.** Microscopic section showing that the airspace enlargement in centriacinar emphysema is most marked adjacent to the abnormal respiratory bronchiole, corresponding to the center of the lobule. Also,

some of the alveolar walls of the abnormal airspaces are thickened and fibrotic (H&E, $\times 16$). **C.** Cut surface of a lung slice showing how the entire lobule is uniformly affected in panacinar emphysema. **D.** Microscopic section demonstrating that in panacinar emphysema, the airspaces adjacent to the lobular septa are enlarged to the same degree as those in the center of the lobule (H&E, $\times 16$).

■ Distal Acinar Emphysema: Paraseptal Emphysema

The original description of distal acinar emphysema is generally credited to Loeschke,³⁴ who described collections of subpleural bullae. It was Heard,^{24,35} however, who first noted that the lesions could extend into the substance of the lung, where they lay along the septa, and coined the term “paraseptal” emphysema. Since the distal part of the acinus (alveolar sacs and ducts) is dominantly involved, emphysema is most striking adjacent to the pleura (superficial emphysema or mantel emphysema), along lobular septa (paraseptal emphysema), at the margins of lobules and acini (periacinar emphysema), and along vessels and airways, which, when cut longitudinally, display a linear pattern. The characteristic morphology is that of multiple contiguous, enlarged airspaces, varying from <0.5 mm to >2 cm in diameter.

Paraseptal emphysema is usually limited in extent and is found most commonly along the anterior and posterior parts of the upper lobe and along the posterior surface of the lower lobe. When extensive, it is usually more severe in the upper half of the lung. Gough has stressed that it is associated with fibrosis of the tissue between

the enlarged airspaces, and this is certainly a common finding.³⁶ Paraseptal emphysema is frequently found in association with centriacinar emphysema,²⁰ but it is most known for its association with spontaneous pneumothoraces in young thin adults.³⁷

■ Irregular Emphysema

Irregular emphysema is logically named, because the acinus is indeed irregularly involved in it. Irregular emphysema is almost invariably adjacent to a scar, giving name to the synonyms *scar* or *paracicatricial emphysema*. Most scars within the lung are usually small and the emphysema is limited in extent. The severity of irregular emphysema depends on the extent of damage to lung tissue, and multiple scars through the lung may lead to multiple foci of irregular emphysema.

DIFFERENTIAL DIAGNOSIS OF EMPHYSEMA

Distinctions among conditions characterized by gas trapping, non-emphysematous airspace enlargement, honeycomb lung, and combined emphysema and fibrosis are considered below.

TABLE 37-1 Differential Diagnosis of Airspace Enlargement

| | Distribution | Enlarged Structure |
|--------------------------|------------------------------------|-------------------------|
| Centrilobular emphysema | Upper lobes, center of lobule | Alveolar ducts, alveoli |
| Panlobular emphysema | Lower lobe, uniform in lobule | Alveoli |
| Paraseptal emphysema | Apical, adjacent to septum | Alveoli |
| Irregular emphysema | No typical site, adjacent to scars | Alveoli |
| Aging | Uniform in lung | Alveolar ducts |
| Compensatory alterations | Uniform in lung | Alveoli |
| Obstructive alterations | Affected area | Alveoli |
| Genetic alterations | Uniform in lung | Lack of septation |
| Asthma | During acute attack | Alveoli |
| Honeycomb lung | Variable—often subpleural | Total remodeling |

■ Gas Trapping

Gas trapping may be seen in a variety of other conditions, not all of which are usually thought of as COPD. The lungs of an asthmatic who has succumbed during an attack are usually characterized by gas trapping, and thus remain inflated, with focal areas of atelectasis (*Table 37-1*). In a patient with long-standing asthma who has died from other causes, or has had a lung resection, there may still be areas of atelectasis. Focal bronchiectasis can be found also, particularly in the anterior segment of the upper lobe. However, parenchymal destruction is not a feature of asthma, and thus gross, microscopic, and morphometric analyses will all be normal in the chronic asthmatic. Gas trapping is also a feature of hypersensitivity pneumonitis and is a feature of connective tissue disease when it involves the small airways.

■ Nonemphysematous Airspace Enlargement

Although not part of the differential diagnosis of COPD, nonemphysematous airspace enlargement also occurs in infancy. In congenital lobar hyperinflation (emphysema), the lobes are overinflated rather than emphysematous, but in some instances, they may be polyalveolar.^{38,39} Some other genetic abnormalities will also give enlarged airspaces, but this is due to failure of septation with a simplified rather than a destroyed alveolar framework.

At the other side of the age spectrum, the term senile emphysema was once used to describe the enlarged airspaces found in the aged. On gross examination, lungs round out with increasing age. An analysis of Gough sections showed increases in anteroposterior distance, height, perimeter, and area of the lung up to the age of 59 years. After this age, only the anteroposterior diameter continued to increase significantly, thus “rounding” the lung dimensions.⁴⁰ This change is due to an increase in the volume proportion of alveolar duct air,⁴¹ with shallower and flatter alveoli,⁴² a process termed *ductectasia*. There is no evidence of lung destruction; thus, the condition does not fulfill the criteria for emphysema.

If a part of the lung collapses or is removed, the remaining lung can expand to fill the increased amount of space available, a process known as *compensatory overinflation*. The exact way that this happens and the limits of the process are unknown. However, no tissue

destruction has occurred, and, by definition, this is not emphysema. It is not clear how much larger the overinflated lung can become, or how it expands to reach the new and larger volume. It is generally thought that the possible extent of overinflation is modest and that all the parts of the acinus are equally expanded.

Obstructive overinflation can occur in adults, and two mechanisms may be involved. In one, the obstruction in the bronchus may act as a ball valve, so that air enters on inspiration but does not leave on expiration. Alternatively, the bronchus may be completely obstructed, and air may be trapped behind channels of collateral ventilation. Whatever the mechanism, the affected part of the lung can expand considerably. Obstructive overinflation differs in a number of ways from compensatory overinflation, although, in both, the lung contains too much air per unit of lung and lung tissue.

■ Honeycomb Lung

The airspace enlargement that occurs in cryptogenic fibrosing alveolitis (usual interstitial pneumonia [UIP]) and other fibrotic lung diseases could possibly be confused with emphysema. While honeycomb spaces are enlarged airspaces, they are the result of parenchymal remodeling with formation of new airspaces, rather than destruction of normal airspaces, and thus have thickened and irregular walls with none of the structure of an acinus. They are lined by bronchiolar epithelium, and often contain mucus; the walls have abundant and well-collagenized connective tissue, which may also contain impressive amounts of muscle and sometimes fat or even bone. There is usually interstitial inflammation in the form of varying degrees of lymphocytic and plasma cell infiltration.

■ Combined Emphysema and Fibrosis

Despite the definition of emphysema, which limits fibrosis, the significance of a mixture of fibrosis and emphysema has been reevaluated in relationship to its clinical, radiologic, and pathologic components.⁴³ The problem is that people who smoke cigarettes not only can develop respiratory bronchiolitis-interstitial lung disease (RB-ILD), but also have a higher incidence of developing UIP (idiopathic interstitial fibrosis), and mixtures of these with emphysema are not uncommon. When the combination of emphysema and UIP occurs, lung volumes can be preserved, but the diffusing capacity becomes markedly decreased, and pulmonary hypertension develops, with its associated significant negative prognosis. CT scans generally show centrilobular or mixed centrilobular and paraseptal emphysema in the upper lobes, with increased reticular markings and honeycomb remodeling in the lower lobes. Pathologically, there is both gross and microscopic emphysema and interstitial fibrosis with fibroblast foci in the areas of active fibrosis.⁴⁴ We have previously reviewed this topic with a focus on the pathologic differential diagnosis (*Fig. 37-5A-D*).⁴⁵ However, whether combined pulmonary fibrosis and emphysema represents a distinct entity or simply represents clustering of the two smoking conditions of emphysema and interstitial fibrosis has not yet been decided.

LESIONS OF THE LARGE AIRWAYS IN COPD

The majority of studies in this area have focused upon the lesions present when the clinical signs and symptoms of chronic bronchitis are also present.

■ Gross Findings

Gross lesions in the large airways are few and subtle. Bronchial pits are the dilated openings of one or more mucus glands into the epithelium. They are most often found along the margins of the cartilaginous rings and at the bifurcations of the airways. In nonbronchitis, the pits can be seen using a hand lens or a dissecting

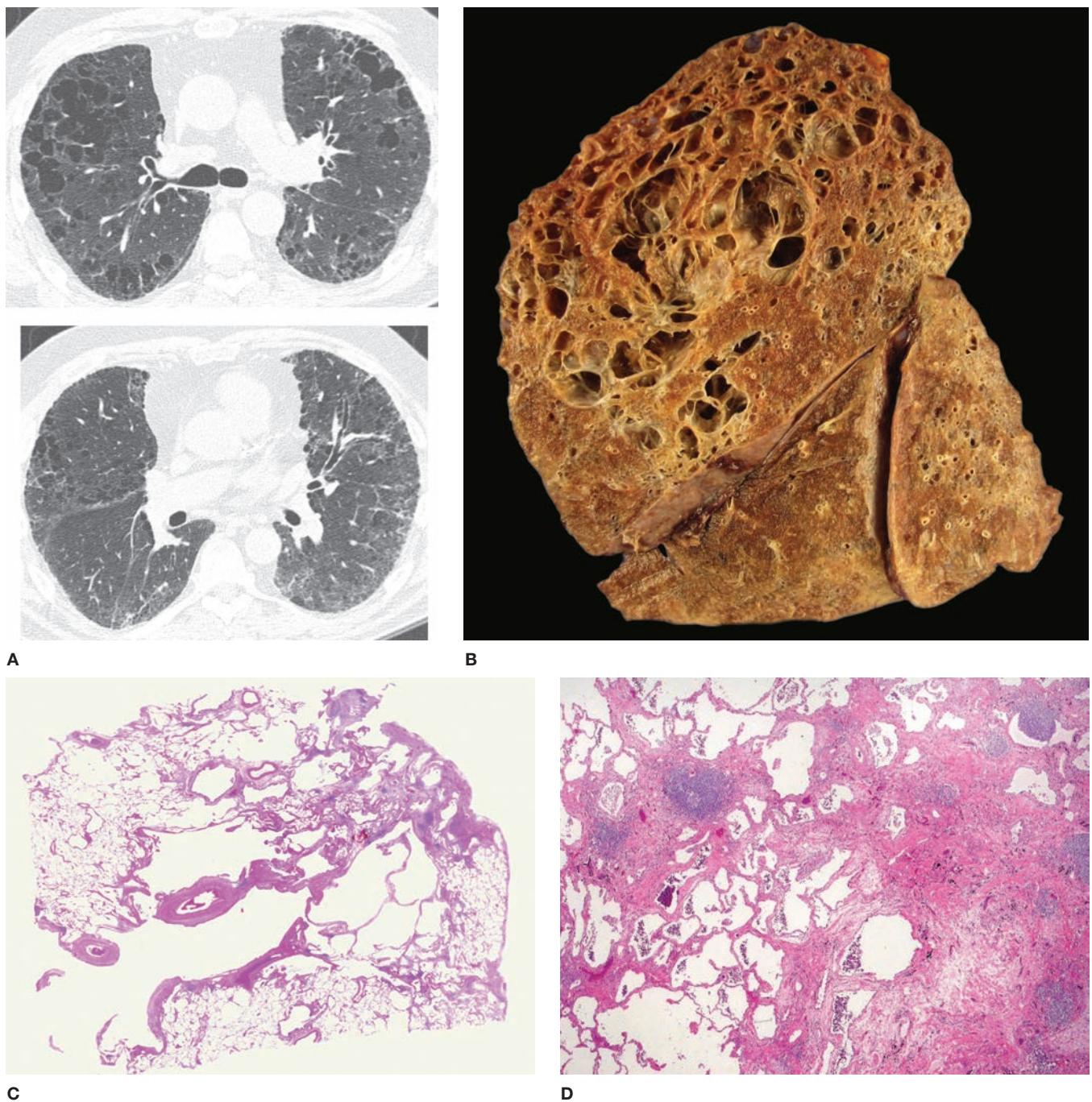


Figure 37-5 Combined fibrosis and emphysema in a case of chronic (fibrotic) hypersensitivity pneumonitis. **A.** Computed tomography scan from upper zone (top) shows emphysema and a suggestive of reticulation; lower image from midlung zone shows extensive reticulation indicating the presence of underlying fibrosis. **B.** Gross photo (sagittal slice) from this case showing marked upper zone emphysema, with fibrosis evident in the most posterior portion of the upper lobe, and the posterior portions of the lower lobe. **C.** Whole mount from the upper lobe. There are large emphysematous spaces, several

with extensive surrounding fibrosis; at higher magnification, many of these fibrotic rims had fibroblast foci (not shown), indicating that this process is really interstitial fibrosis stretched around pre-existing emphysema. **D.** Image from lower lobe showing a UIP-like area, a common finding in chronic hypersensitivity pneumonitis. Elsewhere there were noncaseating granulomas (not shown). (Reproduced with permission from Wright JL, Tazelaar HD, Churg A. Fibrosis with emphysema. *Histopathology*. 2011;58(4):517–524.)

microscope, but in chronic bronchitis, the ducts may be distended with mucus and the mucus may protrude into the lumen of the bronchus and be visible grossly. It is not correct to refer to these as diverticula. First, these are protrusions of normal ducts; and second, they do not extend through all of the muscle coats of the bronchial wall.

While enlarged bronchial pits are the most obvious gross lesions in COPD, careful examination of lung specimens will show that the bronchi do not taper progressively as they approach the pleura,⁴⁶ and they also display prominent circular ridges, probably due to bands of hypertrophic smooth muscle.^{47,48} Gross mucus may be present in the airway lumen, particularly in subjects with chronic bronchitis.⁴⁹

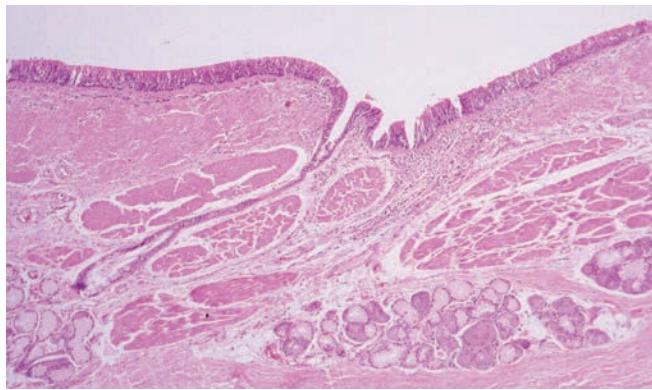


Figure 37-6 Large airway from a subject with chronic bronchitis. The overall wall is thickened with inflammation and fibrosis, and there is prominence of the smooth muscle in addition to the bronchial mucus glands.

■ Microscopic Findings

The intraluminal mucus found in the airways of subjects with COPD contains a mixed population of epithelial cells and acute and chronic inflammatory cells; large numbers of neutrophils can be found during an exacerbation.

Detailed microscopic analysis of the large airways in COPD reveals alterations in the entire airway wall (Fig. 37-6). Epithelial changes are mild in degree and are not necessarily consistent from patient to patient. Epithelial sloughing can occur, but in most instances the epithelium is generally intact and shows only mild goblet cell or squamous cell metaplasia, both of which appear to be more marked if the subject has symptoms of chronic bronchitis.^{50,51} The reticular basement membrane thickness is within the normal range.

The thickness or area of mucus glands in subjects with COPD in general, or chronic bronchitis in particular, is increased over a population mean, but has a distribution that extensively overlaps that of normals and asthmatics.^{52–55} Interestingly, there appears to be a decreased percentage of serous acini in these glands, a feature that apparently does not occur in asthma (discussed below).⁵⁶

Thickening of the inner wall (area internal to the muscular layer) appears to be the most consistent component of airway wall thickening in the large airways of subjects with COPD, and appears to

be generalized.^{57,58} This increase in thickness can be partially attributed to edema and hyperemia of the bronchi,⁵⁹ but is also due to an increase in fibrous tissue or other matrix proteins.

In the large airways of subjects with COPD, increases in the thickness of the muscular layer have not been consistently identified. Although some studies⁶⁰ have found that the average proportion of muscle in main, lobar, and segmental bronchi was approximately doubled in patients with chronic bronchitis and airflow obstruction, others have found that a substantial number of patients fell within the normal range.^{54,55,61}

Alteration in the amount of cartilage in COPD does not appear to be a consistent finding. While some studies^{59,62,63} described cartilage atrophy in chronic bronchitis and/or emphysema, or circumferentially arranged cartilage that extended farther distally in nonbronchitis than bronchitis,⁶⁴ this was not supported by other reports.^{54,65} However, histologic signs of cartilage damage, as judged by loss of cellular or pericellular metachromasia and vacuolated or empty lacunae, can be consistently identified.⁶⁶

The large airways in COPD show a mild, usually mixed, inflammatory infiltrate. Bronchus-associated lymphoid tissue (BALT) is not consistently found, but its frequency appears to be considerably higher (82%) in smokers than nonsmokers (14%).⁶⁷ Bronchial biopsy analysis consistently shows an increase in CD8 T cells, with eosinophils and neutrophils found during exacerbations.^{50,68} Chronic inflammation can also be found around the bronchial glands, particularly in subjects with chronic bronchitis.⁶⁹

■ Differential Diagnosis

A number of common and uncommon disorders constitute the differential diagnosis for airways disease seen in COPD.

Asthma

In asthma the large airways are not dilated, but mucus plugs are classically identified in the large airways of subjects with fatal or near-fatal asthma,⁷⁰ and the mucus may be continuous with that present in the ducts of the mucus glands (Table 37-2). Visible bronchial pits are not a standard feature of asthma, and although the airway wall may be thickened, this is usually not apparent grossly.

In the large airways of subjects with asthma, desquamation of the epithelium is a common feature,^{71,72} and this may be worse in people who have persistent rather than intermittent activity. Sloughing of cohesive epithelial clusters produces the creola bodies found in cytology specimens. Goblet cell metaplasia can be marked in both

TABLE 37-2 Pathologic Differential Diagnosis of Large Airway Lesions in COPD

| | Dilatation | Structural Distortion | Pits | Glands | Submucosal Fibrosis | Basement Membrane | Epithelium | Luminal Mucus | Cartilage | Muscles |
|------------------------------------|------------|---------------------------|-------------|--------|---------------------|-------------------|------------------------------|---------------|-----------|---------|
| Chronic bronchitis | ✓ | Fibrosis and inflammation | ✓ | ✓ | ✓ | X | Goblet cell metaplasia | ✓ | ✓ | ✓/X |
| Asthma | Focal | Focal | X | ✓ | ✓ | ✓ | Goblet cell metaplasia | ✓ | X | ✓ |
| Bronchiectasis | ✓ | Fibrosis and inflammation | ✓ | ✓/X | ✓ | X | Focal goblet cell metaplasia | ✓ | ✓ | X |
| Tracheobronchopathia osteoplastica | ✓ | Bony nodules | X | X | X | X | X | X | ✓ | X |
| Tracheomegaly | ✓ | X | Diverticula | X | X | X | X | X | X | X |
| Relapsing polychondritis | ✓ | ✓ | X | X | X | X | X | X | ✓ | X |

Check mark indicates that the feature is present; X indicates that the feature is absent.

asthma and bronchiectasis,⁷³ but there is a considerable degree of variability, so that this feature cannot be used in isolation to distinguish among the airways of subjects with COPD, asthma, and bronchiectasis. These epithelial cell changes result in an overall thickening of the epithelium in asthma, but not in COPD.⁵⁸ In asthma, the reticular basement membrane (lamina reticularis) is characteristically thickened. This alteration occurs early in the course of disease and remains even when the asthma is mild or well controlled.⁵⁶

The airways of asthmatics demonstrate a greater severity of inner wall thickening, with values double those found in patients with COPD.⁵⁸ The increase in thickness is due to variable increases in fibrous tissue, inflammatory cells, edema fluid, and vascular prominence.^{50,56} Analysis of the muscular wall in subjects with severe or fatal asthma compared with normal subjects or those with COPD shows a marked increase in amount of muscle, with a lesser increase in asthmatics who died with rather than from their asthma.⁷⁴ There has also been a suggestion that the increase in muscle mass may occur relatively early during childhood.⁵⁶

Neutrophils are the predominant cells present in the mucus of patients with bronchiectasis, while eosinophils and accompanying Charcot Leyden crystals are the hallmark of asthmatic mucus. As noted, the cartilaginous destruction present in polychondritis is severe and associated with chronic inflammation, thus easily distinguishing the two processes. Depending upon the severity of the inflammation in bronchiectasis, there may be significant cartilaginous destruction.

Airways from fatal and near-fatal asthma also contain isolated aggregates of lymphoid cells, roughly in the same proportion as that present in COPD.⁷⁵ However, in asthma, by contrast to COPD, there is an inflammatory infiltrate consisting of activated eosinophils, and activated CD4 T cells in the submucosa,⁷⁶ and both mast cells and neutrophils within the glands.⁷⁰ There is little in the literature regarding the inflammatory cell infiltrates present in the airway walls in bronchiectasis. Compared with asthma, there appear to be fewer eosinophils, but a similar population of CD45 (as opposed to any specific subtype) lymphocytes, with both cell types having a greater density in the inner, as opposed to the outer aspect of the airway.⁷⁷

Bronchiectasis

In bronchiectasis, there is, by definition, an abnormal and permanent dilatation of the bronchi; this is usually present to a much greater degree than is found in COPD and is often accompanied by airway distortion. There is exaggeration of the muscular ridges and the presence of multiple bronchial gland-based pits. The large airway walls can be thickened and/or irregularly thinned as a result of inflammation and fibrosis, and there is often inspissated mucus or actual purulent material.

Miscellaneous Conditions

Tracheobronchomegaly (Mounier-Kuhn syndrome) is characterized by a marked dilatation of the trachea and major bronchi, with diameters 5 to 10 cm above normal values.⁷⁸ In this condition there are multiple true diverticula, with outpouchings formed of membranous tracheal tissue between the cartilaginous rings,⁷⁹ with atrophy or absence of elastic fibers.⁸⁰

Patients with tracheobronchopathia osteoplastica have an obstructive pulmonary function pattern,⁸¹ however, unlike the trachea and large airways in COPD, cartilaginous and bony nodules are present in the subepithelial space (submucosa). Relapsing polychondritis^{82,83} shows variable dynamic expiratory and/or inspiratory obstruction depending on the size and location of the airways involved. In this disease, however, the obstruction is due to impaired airway clearance of inflammatory debris, and an ineffective cough because of dynamic upper airway collapse. The airways are dilated and the walls are thickened because of the extensive fibrosis and chronic

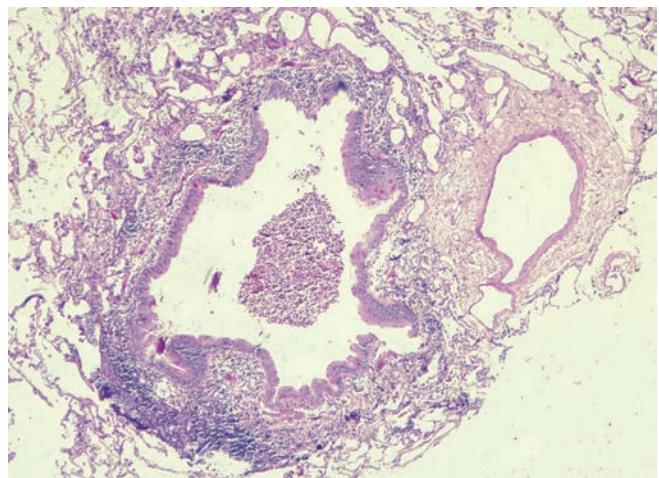


Figure 37-7 A small airway from a subject with COPD. The lumen contains mucus and inflammatory debris. There is goblet cell metaplasia of the epithelium. The subepithelial (submucosal) layer is increased in thickness due to an increase in fibrous tissue and inflammatory cells.

inflammation due to the immunologic nature of this condition. In particular, the cartilaginous plates show extensive destruction.

LESIONS OF THE SMALL AIRWAYS IN COPD

In the context of COPD, small airways refer to airways with an internal diameter of 2 mm or less. In COPD, intraluminal mucus can be found in the small airways, and there appears to be an overall relationship between the degree to which the airways are occluded by mucus and the FEV₁.⁸⁴ Goblet cells are rare in normal small airways, but goblet cell metaplasia is a frequent finding in the airways of patients with COPD.⁸⁵⁻⁸⁷

Similar to the large airways, there is alteration of all of the small airway wall compartments in patients with COPD (Fig. 37-7). These changes result in an overall decrease in the internal bronchiolar diameter and, as assessed by a conformity index, produce significant deformity. Similar results are obtained from three-dimensional reconstructions.⁷⁴ Detailed measurements of the airway walls show that the increased wall thickness is due to increases in the epithelium, subepithelial fibrous tissue compartment (submucosa, lamina propria), smooth muscle, and adventitia.^{58,84} While there is no direct evidence, it seems appropriate that these changes would result in airway obliteration, a process that appears to happen relatively early in airflow obstruction, with the number of airways in patients with severe airflow obstruction reduced to one-tenth of the numbers calculated in the normal lung (Fig. 37-8A, B).⁸⁸ Reduction in airways of 2 to 2.5 mm can be identified using multidetector-row computed tomography (CT), and decreased numbers of terminal bronchioles can be found using a micro-CT approach. Interestingly, this latter technique has also found a decreased luminal area in these airways, again suggesting an obliterative process has occurred.⁸⁹ Although the adventitia is thickened, there is a loss of alveolar attachments to the airway wall,^{90,91} an important process because it allows early airway collapse on expiration.

One of the earliest histologic abnormalities that can be detected in cigarette smokers is the presence of macrophages in the lumen of the respiratory bronchioles.⁹² However, an inflammatory infiltrate can also be identified within the walls of both membranous and respiratory bronchioles in subjects with COPD. When examined in conjunction with the GOLD (Global Strategy for the Diagnosis, Management, and Prevention of COPD) stage, the proportion of airways that had measurable neutrophils appears to be increased in GOLD stages 2 to 4, and airways with measurable macrophages

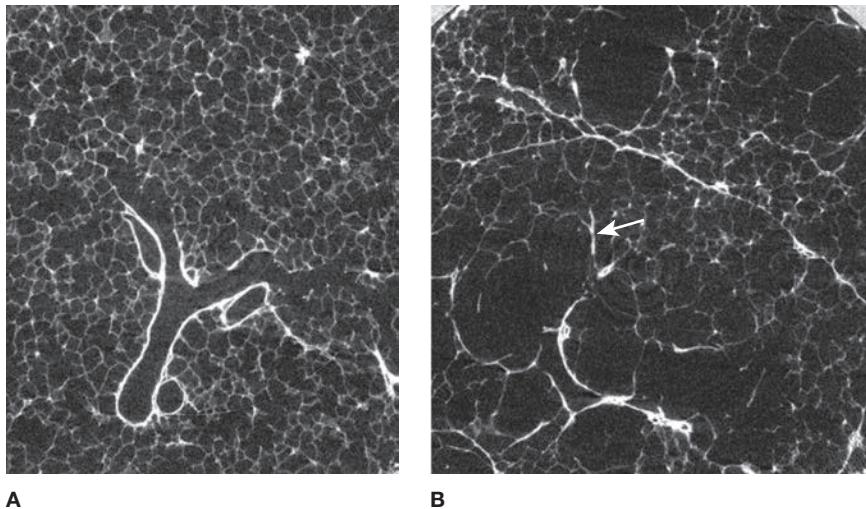


Figure 37-8 **A.** Micro-CT scan image of an airway from a normal lung. Note the regular progression from membranous bronchiole to respiratory bronchiole to alveolar duct. **B.** Micro-CT scan image of an airway from a lung with centrilobular emphysema. Note the irregular airway emptying into a centrilobular hole. Partially obliterated airway is seen at the arrow. (Reproduced with permission from Dr. James C Hogg.)

show a progressive increase from GOLD stage 0 to 4, while there does not seem to be any alteration in the percentage of airways that contain eosinophils among the GOLD stages.⁹³ The percentage of airways with CD4, CD8, and B cells also increase with GOLD stage, but when these data are expressed as total accumulated volume, only the B cells and CD8 cells show progressive increases. The presence of lymphoid follicles is markedly increased in GOLD stages 3 and 4. Interestingly, histone deacetylase 2 (HDAC2) appears to be down-regulated in the small airways of smokers with COPD,⁹⁴ a finding that may be of considerable importance since downregulation of the HDAC system is associated with a proinflammatory cytokine profile.

Differential Diagnosis

A number of important clinical entities constitute the differential diagnosis of small airways disease in COPD.

Asthma

A comparison of the inflammatory and cellular mechanisms present in asthma and COPD has recently been reviewed.⁹⁵ Mucus plugs and goblet cell hyperplasia are markedly increased in the small airways of asthmatics,^{73,96} and this increase is generally much greater than that seen in COPD. In addition, the basement membrane thickness is approximately 20% greater than that found in either normal subjects or patients with COPD.⁷³ The peripheral airways of asthmatics have an inflammatory infiltrate that features lymphocytes and eosinophils,^{73,77,97} with many of the inflammatory cells in the adventitial, as opposed to the submucosal, compartment. The data regarding the vessels in the submucosa are controversial, with some studies suggesting that they are congested, but not increased in number, in asthmatics compared with COPD,⁷⁴ and others demonstrating an increased number of vessels, but a lesser total area in asthma compared with COPD.⁹⁸ Although smooth muscle is increased in asthmatics, the increase is not as great as that present in the large airways.⁹⁹ Moreover, the distribution of smooth muscle increase in the bronchial tree may be quite different, with some patients displaying a generalized increase, while in others the increase is restricted to the larger airways.¹⁰⁰ Overall, the small airways in asthmatic subjects who have died because of their disease have a greater area of subepithelial fibrous tissue, smooth muscle, and adventitial fibrous tissue than do subjects who died with their disease, which in turn have a greater area than do the airways of subjects with COPD.¹⁰¹ Thus, although the same qualitative changes are present in both asthmatics and COPD, they are more severe in asthmatics and most severe in cases of fatal asthma. Interestingly,

there appears to be a loss of alveolar attachments in cases of fatal asthma,¹⁰² although this is less than that present in the airways of patients with COPD.

Follicular Bronchiolitis

Follicular bronchiolitis is characterized by narrowing of the bronchioles due to adventitial and subepithelial lymphoid follicles and accompanied by a lymphoplasmacytic inflammatory infiltrate.¹⁰³ The condition is classically found in patients with rheumatoid arthritis or those with IgA deficiency or common variable immune deficiency. This process can mimic severe COPD small airway disease, but the inflammatory infiltrate is generally magnified compared to COPD, while there is little goblet cell metaplasia in the airway epithelium.

Panbronchiolitis

The presence of foamy macrophages in the airway wall and lumen and extending down into the alveolar ducts and alveoli is a feature of the condition known as panbronchiolitis, originally described in Japan but now known to occur worldwide.^{104,105} Follicular hyperplasia of the peribronchiolar lymphoid tissue is frequent, and bronchiectasis is found in the more advanced lesions.

Constrictive Bronchiolitis

The term *constrictive bronchiolitis* appears to have been coined by Gosink et al.¹⁰⁶ In constrictive bronchiolitis, the airway lumen is occluded by a progressive thickening of the subepithelial (submucosal) space. Both the membranous and respiratory bronchioles are involved and show transmural inflammatory cell infiltrates, occasionally with epithelial necrosis. Mucus plugs also can be identified. As the process evolves, the inflammatory infiltrate wanes, and greater amounts of fibrous tissue can be demonstrated both in the peribronchial and subepithelial portions of the airway, acting to narrow or obliterate the airway lumen.¹⁰⁷ Lesions of constrictive bronchiolitis, particularly in the organized phase, may be difficult to demonstrate and may require elastic stains to outline the obliterated airway. Thus, the lesions in COPD differ from constrictive bronchiolitis only in degree.

Mineral dust-induced airway disease is a distinctive type of constrictive bronchiolitis, characterized by a stereotypic response of the small airways to high doses of particulate, regardless of the specific mineral dust involved. The lesions consist of fibrosis and thickening of the walls of both the membranous and respiratory bronchioles, sometimes extending down the alveolar ducts, the latter finding providing diagnostic discrimination from tobacco

smoke-induced airway disease, which tends not to involve the alveolar ducts. Pigment deposition is highly variable and is not a diagnostic feature.¹⁰⁶ Other forms of constrictive bronchiolitis may be related to ingestion of toxic compounds such as *Sauvopis androgynus* ingestion,^{109–112} or related to diffuse neuroendocrine cell hyperplasia.^{113–116}

Proliferative Bronchiolitis

The lesions of proliferative bronchiolitis have been elegantly described and illustrated.^{115–117} Within the lumens of the membranous and respiratory bronchioles are plugs of organizing fibroblastic (granulation) tissue. Occasionally, ulceration of the epithelium can be seen, and early lesions may have fibrin. The granulation tissue is formed of a pale matrix with proliferating spindle cells, accompanied by chronic inflammatory cells. As the lesions age, the granulation tissue usually shrinks and contracts. However, in a certain proportion of cases, the bronchiolar cells proliferate over the granulation tissue and incorporate it into the subepithelial space, leaving an irregular airway lumen.

Although acute bronchiolitis, be it bacterial or viral in nature, is usually easily distinguished from the lesions of COPD by the presence of extensive epithelial damage, healed lesions may show nonspecific airway fibrosis and chronic inflammation, or the residua of proliferative bronchiolitis. Interestingly, latent adenoviral infection has been suggested as a contributor to airflow obstruction in adults by amplifying the inflammatory response in the bronchioles of cigarette smokers.¹²⁰ Airway disease complicating other diseases may also need to be distinguished from that of COPD. For example, posttransplant bronchiolitis^{118,121} or airway disease in patients with inflammatory bowel disease (both Crohn disease and ulcerative colitis)¹²² include both proliferative and constrictive bronchiolitis. Inflammatory bowel disease may also have large airway involvement.

LESIONS OF THE VESSELS IN COPD

There are no consistent alterations in the large elastic pulmonary arteries of subjects with COPD. Atheromata can be found,¹²³ but unless there is pulmonary hypertension, the incidence is probably not greater than that found in a carefully matched population.

Cigarette smokers, with or without pulmonary hypertension, have an increase in arterial muscle media thickness as well as intimal fibrosis in the muscular arteries, and progressive muscularization of the small arterioles.¹²² Increases in intimal thickness with longitudinal muscle formation are a common feature in lungs of patients with COPD (Fig. 37-9).^{11,125,126} There appears to be a progressive increase

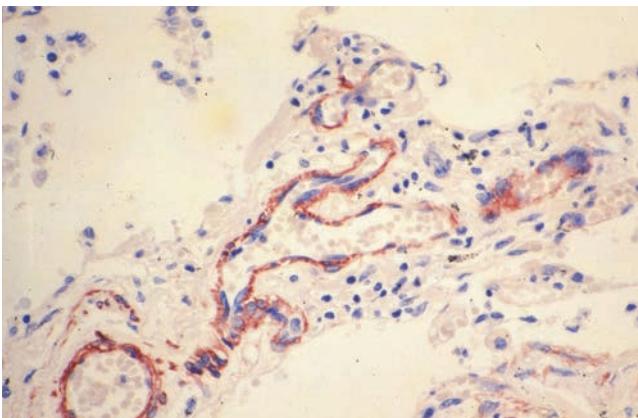


Figure 37-9 A small pulmonary artery from a subject with COPD. These vessels, situated adjacent to the alveolar ducts, are normally poorly muscularized, but in this case, the vessel has a distinct circumferential muscular layer.

in the numbers of smaller muscularized arteries, percent medial thickness, and percent intimal thickness of muscularized arteries from nonsmokers, to smokers without obstruction, to smokers with airflow obstruction.¹²⁷

The lesions of primary pulmonary hypertension and hypertension secondary to vascular shunting also include intimal fibrosis and increased muscular media thickness. Intimal fibrosis is often cellular in its early phases, but progresses to concentric laminar fibrosis, which can almost totally obliterate the vessel lumen. These changes are of much greater severity than those identified secondary to COPD. Vasculitis, fibrinoid necrosis, and plexiform lesions are never found in COPD. Lesions of chronic thromboembolic disease include eccentric intimal thickening and the occasional formation of webs due to recanalization of the thrombi.

NONPATHOLOGIC, CT SCAN-BASED, EVALUATION OF TISSUE COMPARTMENTS IN COPD

CT scanning has provided useful information on the lung parenchyma, airways, and pulmonary vasculature in patients with COPD.

■ Emphysema

The advent of high-resolution CT scanners has allowed identification of even mild emphysema and can distinguish between emphysema and senile lung airspace enlargement. When combined with general morphometric principles, emphysema can be quantified, and emphysema progression can be monitored.^{128–131}

■ Airways

Evaluation of this compartment is in its developmental phase, with much of the work being performed on phantom airways or in large animals. In humans, thin-section CT scans are able to demonstrate evidence of airway wall remodeling in the more proximal airways (first- to sixth-generation airways) of subjects with COPD or asthma, and it has been suggested that changes in these airways can be extrapolated to the smaller airways.¹³² Use of multidetector-row CT has extended these data.⁸⁹ Certainly, the data do suggest that these measurements correlate with lung physiology, independent from emphysema.¹³³

■ Pulmonary Arteries

Measurements of the mainstem pulmonary artery are easily performed on CT scans using contrast, and these data have shown prognostic significance. Evaluation of the smaller vessels is much more difficult, but initial work has found that determination of the total cross-sectional area of the vessels that have an individual cross-sectional area of less than 5 mm² has a significant negative correlation with pulmonary arterial pressure, at least in patients with severe emphysema.^{134,135}

SUMMARY

There are a number of pathologic alterations of the lung in COPD. These involve almost all of the lung compartments, including the parenchyma, vasculature, and large and small airways. These changes can overlap the pathologic findings present in other diseases associated with airflow obstruction, or other diseases that are manifested in the lung. It is important to be able to make the distinction among these diseases. Although the pathologic alterations roughly correlate to alterations in pulmonary function, it is important to remember that their individual contributions are not well worked out. Thus, it may be difficult on an individual patient basis to proceed from a clinical classification such as the GOLD classification to a mechanistic/pathologic explanation of the airflow obstruction. Advances in CT scanning technology have allowed evaluation and quantification of emphysema, and there is developing work

suggesting that evaluation of the airways and pulmonary arterial system also may be possible.

REFERENCES

- Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med.* 2017;195:557–582.
- Bonet T. *Sepulchretum Sive Anatomia Practica ex Cadaveribus morbo denatis, proponens historias observationes omnium pene humani corporis affectuum, ipsorumque causas reconditas revelans.* Geneva: 1679.
- Morgagni GB. The Seats and Causes of Disease. Investigated by Anatomy; in Five Books, Containing a Great Variety of Dissections, with Remarks. London: Johnson and Payne; 1769.
- Ruysh F. *Observationes Anatomica-Chirurgicae. Tractatio Anatomica.* Amsterdam: 1721.
- Baillie M. *A Series of Engravings, Accompanied with Explanations Which are Intended to Illustrate the Morbid Anatomy of Some of the Most Important Parts of the Human Body Divided into 10 Fascicule.* London: W. Bulmer and Co; 1799.
- Baillie M. *The Morbid Anatomy of Some of the Most Important Parts of the Human Body.* 3rd ed. London: W. Bulmer and Co; 1807.
- Laennec RTH. *A Treatise on the Diseases of the Chest and on Mediate Auscultation.* London: T. and G. Underwood; 1834.
- Gough J. The pathological diagnosis of emphysema. *Proc R Soc Med.* 1952;45:576–577.
- Gough J, Wentworth JE. The use of thin sections of entire organs in morbid anatomical studies. *J R Microsc Soc.* 1949;69: 231–235.
- McLean KH. The histology of generalized pulmonary emphysema. I. The genesis of the early centrilobular lesion: focal emphysema. *Australas Ann Med.* 1957;6:124–140.
- McLean KH. The significance of pulmonary vascular changes in emphysema. *Australas Ann Med.* 1958;7:69–84.
- Ciba Guest Symposium. Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions. *Thorax.* 1959;14:286–299.
- World Health Organization. Chronic cor pulmonale: report of an expert committee: technical Report Series. *Circulation.* 1963;27:594–615.
- American Thoracic Society. Chronic bronchitis, asthma, and pulmonary emphysema: a statement by the committee on diagnostic standards for nontuberculous respiratory diseases. *Am Rev Respir Dis.* 1962;85:762–768.
- Medical Research Council. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet.* 1965;1:775–779.
- Snider GL, Thurlbeck WM, Bengali ZH. The definition of emphysema. Report of a national heart lung and blood institute division of lung diseases workshop. *Am Rev Respir Dis.* 1985;132:182–185.
- Leopold JG, Gough J. The centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. *Thorax.* 1957;12:219–235.
- Wyatt JP, Fischer VW, Sweet H. Centrilobular emphysema. *Lab Invest.* 1961;10:159–177.
- Snider GL, Brody JS, Doctor L. Subclinical pulmonary emphysema Incidence and anatomic patterns. *Am Rev Respir Dis.* 1966;21:155–166.
- Thurlbeck WM. The incidence of pulmonary emphysema with observations on the relative incidence and spatial distribution of various types of emphysema. *Am Rev Respir Dis.* 1963;87:206–215.
- Hernandez JA, Anderson AE Jr, Holmes WL, Foraker AG. Macroscopic relations in emphysematous and aging lungs. *Geriatrics.* 1966;21:155–166.
- Bignon J, Andre-Bougaran J, Brouet G. Parenchymal, bronchiolar and bronchial measurements in centrilobular emphysema. Relation to weight of right ventricle. *Thorax.* 1970;25:556–567.
- Mitchell RS, Silvers GW, Goodman N, et al. Are centrilobular emphysema and panlobular emphysema two different diseases? *Hum Pathol.* 1970;1:433–441.
- Heard BE. Further observations on the pathology of pulmonary emphysema in chronic bronchitis. *Thorax.* 1959;14:58–70.
- Cosio MG, Shiner RJ, Saetta M, et al. Alveolar fenestrae in smokers. *Am Rev Respir Dis.* 1986;133:126–131.
- Nagai A, Inano H, Matsuba K, Thurlbeck WM. Scanning electronmicroscopic morphometry of emphysema in humans. *Am J Respir Crit Care Med.* 1994;150:1411–1415.
- Eidelman D, Saetta M, Ghezzo H, et al. Cellularity of the alveolar walls in smokers and its relation to alveolar destruction. *Am Rev Respir Dis.* 1990;141:1547–1552.
- Retamales I, Elliott WM, Meshi B, et al. Amplification of inflammation in emphysema and its association with latent adenoviral infection. *Am J Respir Crit Care Med.* 2001;164: 469–473.
- Cardoso WV, Sekhon HS, Hyde DM, Thurlbeck WM. Collagen and elastin in human pulmonary emphysema. *Am Rev Respir Dis.* 1993;147:975–981.
- Lang MR, Fiaux GW, Gillooly M, et al. Collagen content of alveolar wall tissue in emphysematous and non-emphysematos lungs. *Thorax.* 1994;49:319–326.
- Lang MR, Fiaux GW, Hulmes DJ, et al. Quantitative studies of human lung airspace wall in relation to collagen and elastin content. *Matrix.* 1993;13:471–480.
- Kuhn C 3rd, Tavassoli F. The scanning electron microscopy of elastase-induced emphysema. *Lab Invest.* 1976;34:2–9.
- Laurell CB, Eriksson S. The electrophoretic a1-globulin pattern of serum in a1-antitrypsin deficiency. *Scand J Clin Lab Invest.* 1963;15:132–140.
- Loeschke H. Sotrungen des Luftgehalts. In: Henke F, Lubarsch O, eds. *Atmungswege und Lungen: Handbuch der speziellen Pathologische Anatomie und Histologie.* Berlin: Springer-Verlag; 1928:640–641.
- Heard BE. A pathological study of emphysema of the lungs with chronic bronchitis. *Thorax.* 1958;13:136–149.
- Gough J. The pathogenesis of emphysema. In: Liebow AA, Smith DE, eds. *The Lung.* Baltimore, MD: Williams and Wilkins; 1968:109–133.
- Lindskog GE, Halasz NA. Spontaneous pneumothorax: a consideration of pathogenesis and management with review of seventy-two hospitalized cases. *AMA Arch Surg.* 1957;75:693–698.
- Tapper D, Schuster S, McBride J, et al. Polyalveolar lobe: anatomic and physiologic parameters and their relationship to congenital lobar emphysema. *J Pediatr Surg.* 1980;15:931–937.
- Hislop A, Reid LM. New pathological findings in emphysema of childhood. 2. Overinflation of a normal lobe. *Thorax.* 1971;26:190–194.

40. Anderson WF, Anderson AE, Hernandez JA, Foraker AG. Topography of aging and emphysematous lungs. *Am Rev Respir Dis.* 1964;90: 411–423.
41. Angus GE, Thurlbeck WM. Number of alveoli in the human lung. *J Appl Physiol.* 1972;32:483–485.
42. Ryan SF, Vincent TN, Mitchell RS, et al. Ductectasia; an asymptomatic pulmonary change related to age. *Med Thorac.* 1965;22:181–187.
43. Cottin V. Combined pulmonary fibrosis and emphysema: bad and ugly all the same?. *Eur Respir J.* 2017;50: 1700846
44. Kawabata Y, Hoshi E, Murai K, et al. Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to postoperative course. *Histopathology.* 2008;53:707–714.
45. Wright JL, Tazelaar H, Churg A. Fibrosis with Emphysema. *Histopathology.* 2011;58:517–524.
46. Restrepo GL, Heard BE. Air trapping in chronic bronchitis and emphysema. Measurements of the bronchial cartilage. *Am Rev Respir Dis.* 1964;90:395–400.
47. Wang NS, Ying WL. The pattern of goblet cell hyperplasia in human airways. *Hum Pathol.* 1977;8:301–311.
48. Wang NS, Ying WL. Morphogenesis of human bronchial diverticulum. A scanning electron microscopic study. *Chest.* 1976;69:201–204.
49. Aikawa T, Shimura S, Sasaki H, et al. Morphometric analysis of intraluminal mucus in airways in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1989;140:477–482.
50. Jeffery PK. Comparison of the structural and inflammatory features of COPD and asthma. Giles F. Filley Lecture. *Chest.* 2000;117:251S–260S.
51. Trevisani L, Sartori S, Bovolenta MR, et al. Structural characterization of the bronchial epithelium of subjects with chronic bronchitis and in asymptomatic smokers. *Respiration.* 1992;59:136–141.
52. Thurlbeck WM, Angus GE. A distribution curve for chronic bronchitis. *Thorax.* 1964;19:436–442.
53. Thurlbeck WM, Angus GE, Pare JP. Mucous gland hypertrophy in chronic bronchitis, and its occurrence in smokers. *Br J Dis Chest.* 1963;57:73–78.
54. Takizawa T, Thurlbeck WM. Muscle and mucous gland size in the major bronchi of patients with chronic bronchitis, asthma and asthmatic bronchitis. *Am Rev Respir Dis.* 1971;104: 331–336.
55. Dunnill MS, Massarella GR, Anderson JA. A comparison of the quantitative anatomy of the bronchi in normal subjects in status asthmaticus in chronic bronchitis and in emphysema. *Thorax.* 1969;24:176–179.
56. Jeffery PK. Remodeling in asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med.* 2001;164:528–538.
57. Tiddens HA, Pare PD, Hogg JC, et al. Cartilaginous airway dimensions and airflow obstruction in human lungs. *Am J Respir Crit Care Med.* 1995;152:260–266.
58. Pare PD, Wiggs BR, James A, et al. The comparative mechanics and morphology of airways in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1991;143:1189–1193.
59. Wright RR, Stuart CM. Chronic bronchitis with emphysema: a pathological study of the bronchi. *Med Thorac.* 1965;22: 210–218.
60. Carlile A, Edwards C. Structural variation in the named bronchi of the left lung: a morphometric study. *Br J Dis Chest.* 1983;77:344–348.
61. Nagai A, West WW, Paul JL, Thurlbeck WM. The National Institutes of Health intermittent positive pressure breathing trials: pathology studies. I. Interrelationship between morphologic lesions. *Am Rev Respir Dis.* 1985;132:937–945.
62. Wright RR. Bronchial atrophy and collapse in chronic obstructive pulmonary emphysema. *Am J Pathol.* 1960;37:63–77.
63. Thurlbeck WM, Pun R, Toth J, Fraser RG. Bronchial cartilage in chronic obstructive lung disease. *Am Rev Respir Dis.* 1974;109:73–80.
64. Tandon MK, Campbell AH. Bronchial cartilage in chronic bronchitis. *Thorax.* 1969;27:607–612.
65. Greenberg SD, Boushy SF, Jenkins DE. Chronic bronchitis and emphysema: correlation of pathologic findings. *Am Rev Respir Dis.* 1967;96:918–928.
66. Haraguchi M, Shimura S, Shirato K. Morphometric analysis of bronchial cartilage in chronic obstructive pulmonary disease and bronchial asthma. *Am J Respir Crit Care Med.* 1999;159:1005–1013.
67. Richmond I, Pritchard GE, Ashcroft T, et al. Bronchus associated lymphoid tissue (BALT) in human lung: its distribution in smokers and non smokers. *Thorax.* 1993;48:1130–1134.
68. Turato G, Zuin R, Saetta M. Pathogenesis and pathology of COPD. *Respiration.* 2001;68:117–128.
69. Mullen JB, Wright JL, Wiggs BR, et al. Reassessment of inflammation of airways in chronic bronchitis. *Br Med J (Clin Res Ed).* 1985;291:1235–1239.
70. Carroll NG, Mutavdzic S, James AL. Increased mast cells and neutrophils in submucosal mucous glands and mucus plugging in patients with asthma. *Thorax.* 2002;57:677–682.
71. Jeffery PK, Wardlaw AJ, Nelson FC, et al. Bronchial biopsies in asthma. An ultrastructural, quantitative study and correlation with hyperreactivity. *Am Rev Respir Dis.* 1989;140:1745–1753.
72. Laitinen A, Laitinen LA. Airway morphology: epithelium/basement membrane. *Am J Respir Crit Care Med.* 1994;150: S14–S17.
73. Haraguchi M, Shimura S, Shirato K. Morphologic aspects of airways of patients with pulmonary emphysema followed by bronchial asthma-like attack. *Am J Respir Crit Care Med.* 1996;153:638–643.
74. Thurlbeck WM, Wright JL. *Thurlbeck's Chronic Airflow Obstruction.* 2nd ed. Hamilton, ON: B.C. Decker; 1999.
75. Elliot JG, Jensen CM, Mutavdzic S, et al. Aggregations of lymphoid cells in the airways of nonsmokers, smokers, and subjects with asthma. *Am J Respir Crit Care Med.* 2004;169:712–718.
76. Fabbri LM, Romagnoli M, Corbetta L, et al. Differences in airway inflammation in patients with fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2003;167:418–424.
77. Haley KJ, Sunday ME, Wiggs BR, et al. Inflammatory cell distribution within and along asthmatic airways. *Am J Respir Crit Care Med.* 1998;158:565–572.
78. Katz I, LeVine M, Herman P. Tracheobronchiomegaly: the Mounier-Kuhn syndrome. *Am J Roentgenol Radium Ther Nucl Med.* 1962;88:1084–1094.
79. Woodring JH, Howard RS 2nd, Rehm SR. Congenital tracheobronchomegaly (Mounier-Kuhn syndrome): a report of 10 cases and review of the literature. *J Thorac Imaging.* 1991;6:1–10.
80. Van Schoor J, Joos G, Pauwels R. Tracheobronchomegaly: the Mounier-Kuhn syndrome. *Eur Respir J.* 1991;4:1303–1306.

81. Lundgren R, Stjernberg NL. Tracheobronchopathia osteochondroplastica. A clinical bronchoscopic and spirometric study. *Chest*. 1981;80:706–709.
82. Littlewood JM. Update on the United States epidemiology study. *Postgrad Med J*. 1996;72:S6.
83. Mohsenifar Z, Tashkin DP, Carson SA, Bellamy PE. Pulmonary function in patients with relapsing polychondritis. *Chest*. 1982;81:711–717.
84. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:2645–2653.
85. Wright JL, Lawson LM, Paré PD, et al. The detection of small airways disease. *Am Rev Respir Dis*. 1984;129:989–994.
86. Wright JL, Lawson LM, Pare PD, et al. Morphology of peripheral airways in current smokers and ex-smokers. *Am Rev Respir Dis*. 1983;127:474–477.
87. Saetta M, Turato G, Baraldo S, et al. Goblet cell hyperplasia and epithelial inflammation in peripheral airways of smokers with both symptoms of chronic bronchitis and chronic airflow limitation. *Am J Respir Crit Care Med*. 2000;161:1016–1021.
88. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med*. 2011;365:1567–1575.
89. Tanabe N, Vasilescu DM, Kirby M, et al. Analysis of airway pathology in COPD using a combination of computed tomography, micro-computed tomography and histology. *Eur Respir J*. 2018;51:1701245
90. Tanabe N, Vasilescu DM, McDonough JE, et al. Micro-computed tomography comparison of preterminal bronchioles in centrilobular and panlobular emphysema. *Am J Respir Crit Care Med*. 2017;195(5):630–638.
91. Saetta M, Ghezzo H, King M, et al. Loss of alveolar attachments in smokers. A morphometric correlate of lung function impairment. *Am Rev Respir Dis*. 1985;132:894–900.
92. Niewoehner DE, Kleinerman J, Rice DB. Pathologic changes in the peripheral airways of young cigarette smokers. *N Engl J Med*. 1974;291:755–758.
93. National Heart Lung and Blood Institute, World Health Organization. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: NHLBI/WHO Workshop*. 2001.
94. Isajevs S, Taivans I, Svirina D, et al. Patterns of inflammatory responses in large and small airways in smokers with and without chronic obstructive pulmonary disease. *Respiration*. 2011;81:362–371.
95. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. *Clin Sci (Lond)*. 2017;131(13):15411558.
96. Aikawa T, Shimura S, Sasaki H, et al. Marked goblet cell hyperplasia with mucus accumulation in the airways of patients who died of severe acute asthma attack. *Chest*. 1992;101:916–921.
97. Carroll N, Cooke C, James A. The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics. *Eur Respir J*. 1997;10:292–300.
98. Hashimoto M, Tanaka H, Abe S. Quantitative analysis of bronchial wall vascularity in the medium and small airways of patients with asthma and COPD. *Chest*. 2005;127:965–968.
99. Carroll NG, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis*. 1993;147:405–410.
100. Ebina M, Yaegashi H, Chiba R, et al. Hyperreactive site in the airway tree of asthmatic patients revealed by thickening of bronchial muscles. *Am Rev Respir Dis*. 1990;141:1327–1332.
101. Kuwano K, Bosken CH, Pare PD, et al. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1993;148:1220–1225.
102. Mauad T, Silva LF, Santos MA, et al. Abnormal alveolar attachments with decreased elastic fiber content in distal lung in fatal asthma. *Am J Respir Crit Care Med*. 2004;170:857–862.
103. Wells AU, deBois RM. Bronchiolitis in association with connective tissue disorders. In: King TE, ed. *Bronchiolitis*. Philadelphia, PA: W.B. Saunders; 1993:655–666.
104. Iwata M, Sato A, Colby TV. Diffuse panbronchiolitis. In: Epler GR, ed. *Diseases of the Bronchioles*. New York, NY: Raven; 1994:153–180.
105. Kitaichi M. Comparative pathology of inflammatory airways disease: a report made after the 1987 Milan congress. *Sarcoidosis*. 1992;9:625–628.
106. Gosink BB, Friedman PJ, Liebow AA. Bronchiolitis obliterans. Roentgenologic pathologic correlation. *Am J Roentgenol Radium Ther Nucl Med*. 1973;117:816–832.
107. Colby TV, Myers JL. Clinical and histologic spectrum of bronchiolitis obliterans, including bronchiolitis obliterans organizing pneumonia. *Sem Respir Med*. 1992;13:119–133.
108. Churg A, Wright JL. Small airways disease caused by mineral dusts. *Appl Occup Environ Hyg*. 1998;13:617–620.
109. Lai RS, Chiang AA, Wu MT, et al. Outbreak of bronchiolitis obliterans associated with consumption of *Sauvopus androgynus* in Taiwan. *Lancet*. 1996;348:83–85.
110. Lin TJ, Lu CC, Chen KW, Deng JF. Outbreak of obstructive ventilatory impairment associated with consumption of *Sauvopus androgynus* vegetable. *J Toxicol Clin Toxicol*. 1996;34:1–8.
111. Ger LP, Chiang AA, Lai RS, et al. Association of *Sauvopus androgynus* and bronchiolitis obliterans syndrome: a hospital-based case-control study. *Am J Epidemiol*. 1997;145:842–849.
112. Hsieh TR, Guo YL, Chen KW, et al. Dose-response relationship and irreversible obstructive ventilatory defect in patients with consumption of *Sauvopus androgynus*. *Chest*. 1998;113:71–76.
113. Davies S, Gosney J, Hansell D, et al. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: an under-recognised spectrum of disease. *Thorax*. 2007;62:248–252.
114. Aguayo SM, Miller YE, Waldron JA, et al. Brief report: idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease. *N Engl J Med*. 1992;327:1285–1288.
115. Armas OA, White DA, Erlandson RA, Rosai J. Diffuse idiopathic pulmonary neuroendocrine cell proliferation presenting as interstitial lung disease. *Am J Surg Pathol*. 1995;19:963–970.
116. Miller RR, Muller NL. Neuroendocrine cell hyperplasia and obliterative bronchiolitis in patients with peripheral carcinoid tumors. *Am J Surg Pathol*. 1995;19:653–658.
117. Myers JL, Colby TV. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. In: King TE, ed. *Bronchiolitis*. Philadelphia, PA: W.B. Saunders; 1993:611–622.
118. Wright JL, Cagle P, Churg A, et al. Diseases of the small airways. *Am Rev Respir Dis*. 1992;146:240–262.
119. Colby TV. Bronchiolar pathology. In: Epler GR, ed. *Diseases of the Bronchioles*. New York, NY: Raven; 1994:77–100.

120. Matsuse T, Hayashi S, Kuwano K, et al. Latent adenoviral infection in the pathogenesis of chronic airways obstruction. *Am Rev Respir Dis.* 1992;146:177–184.
121. Paradis I, Yousem S, Griffith B. Airway obstruction and bronchiolitis obliterans after lung transplantation. In: King TE, ed. *Bronchiolitis.* Philadelphia, PA: W.B. Saunders; 1993:750–764.
122. Camus P, Piard F, Ashcroft T, et al. The lung in inflammatory bowel disease. *Medicine (Baltimore).* 1993;72:151–183.
123. Dunnill MS. An assessment of the anatomical factor in cor pulmonale in emphysema. *J Clin Pathol.* 1961;14:246–258.
124. Wright JL, Levy RD, Churg A. Pulmonary hypertension in chronic obstructive pulmonary disease: current theories of pathogenesis and their implications for treatment. *Thorax.* 2005;60:605–609.
125. Naeye RL, Greenberg D, Valdivia E. Small pulmonary vessels in advanced pulmonary emphysema. *Arch Pathol Lab Med.* 1974;97:216–220.
126. Hicken P, Heath D, Brewer DB, Whitaker W. The small pulmonary arteries in emphysema. *J Pathol Bacteriol.* 1965;90:107–114.
127. Hale KA, Ewing SL, Gosnell BA, Niewoehner DE. Lung disease in long-term cigarette smokers with and without chronic airflow obstruction. *Am Rev Respir Dis.* 1984;130: 716–721.
128. Gorbunova V, Jacobs SS, Lo P, et al. Early detection of emphysema progression. *Med Image Comput Assist Interv.* 2010;13: 193–200.
129. Gierada DS, Bierhals AJ, Choong CK, et al. Effects of CT section thickness and reconstruction kernel on emphysema quantification relationship to the magnitude of the CT emphysema index. *Acad Radiol.* 2010;17:146–156.
130. Bellia M, Benfante A, Menozzi M, et al. Validation of lung densitometry threshold at CT for the distinction between senile lung and emphysema in elderly subjects. *Monaldi Arch Chest Dis.* 2011;75:162–166.
131. Yuan R, Nagao T, Pare PD, et al. Quantification of lung surface area using computed tomography. *Respir Res.* 2010;11:153.
132. Nakano Y, Muro S, Sakai H, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med.* 2000;162:1102–1108.
133. Mair G, Maclay J, Miller JJ, et al. Airway dimensions in COPD: relationships with clinical variables. *Respir Med.* 2010;104: 1683–1690.
134. Matsuoka S, Washko GR, Yamashiro T, et al. Pulmonary hypertension and computed tomography measurement of small pulmonary vessels in severe emphysema. *Am J Respir Crit Care Med.* 2010;181:218–225.
135. Matsuoka S, Washko GR, Dransfield MT, et al. Quantitative CT measurement of cross-sectional area of small pulmonary vessel in COPD: correlations with emphysema and airflow limitation. *Acad Radiol.* 2012;17:93–99.

CHAPTER 38

Chronic Obstructive Pulmonary Disease: Epidemiology, Pathophysiology, Pathogenesis

Takudzwa Mkorombindo

Mark T. Dransfield

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities. The causative agent is usually significant exposure to noxious particles or gases and

influenced by host factors, including abnormal lung development.¹ COPD includes a spectrum of pathology that involves damage to the lung parenchyma (emphysema) and abnormalities of the tracheobronchial tree (bronchitis). The manifestation of the disease varies greatly, and despite the knowledge acquired in the past 300 years, our understanding of factors that influence disease phenotypes remains incomplete. In the 16th and 17th centuries, we had the earliest descriptions of COPD, with the description of emphysematous lungs as “voluminous lungs.”² Later, chronic bronchitis and other features were identified. While different clinical and biologic phenotypes exist, airflow obstruction characterized using spirometry is the hallmark.

Spirometry is essential in the diagnosis and is beneficial for prognostication and monitoring treatment outcomes. The most accepted criteria for airflow obstruction by spirometry is a reduction of the post-bronchodilator FEV₁/FVC ratio below 0.7. While the 0.7 cutoff value for the FEV₁/FVC ratio may underrecognize patients in the early stages and may overdiagnose disease in healthy middle-aged and older individuals, it has been the most accepted because it balances disease detection sensitivity and specificity.^{3–6} Historically, further classification of severity was based strictly on airflow limitation. Over the past decade, guidelines have evolved to incorporate a multimodality assessment of symptom burden and exacerbation risk (Fig. 38-1). Additionally, there has been an interest in going beyond symptom burden (dyspnea and history of exacerbations) to incorporate the different chest imaging patterns.⁷ Chapter 40 comments

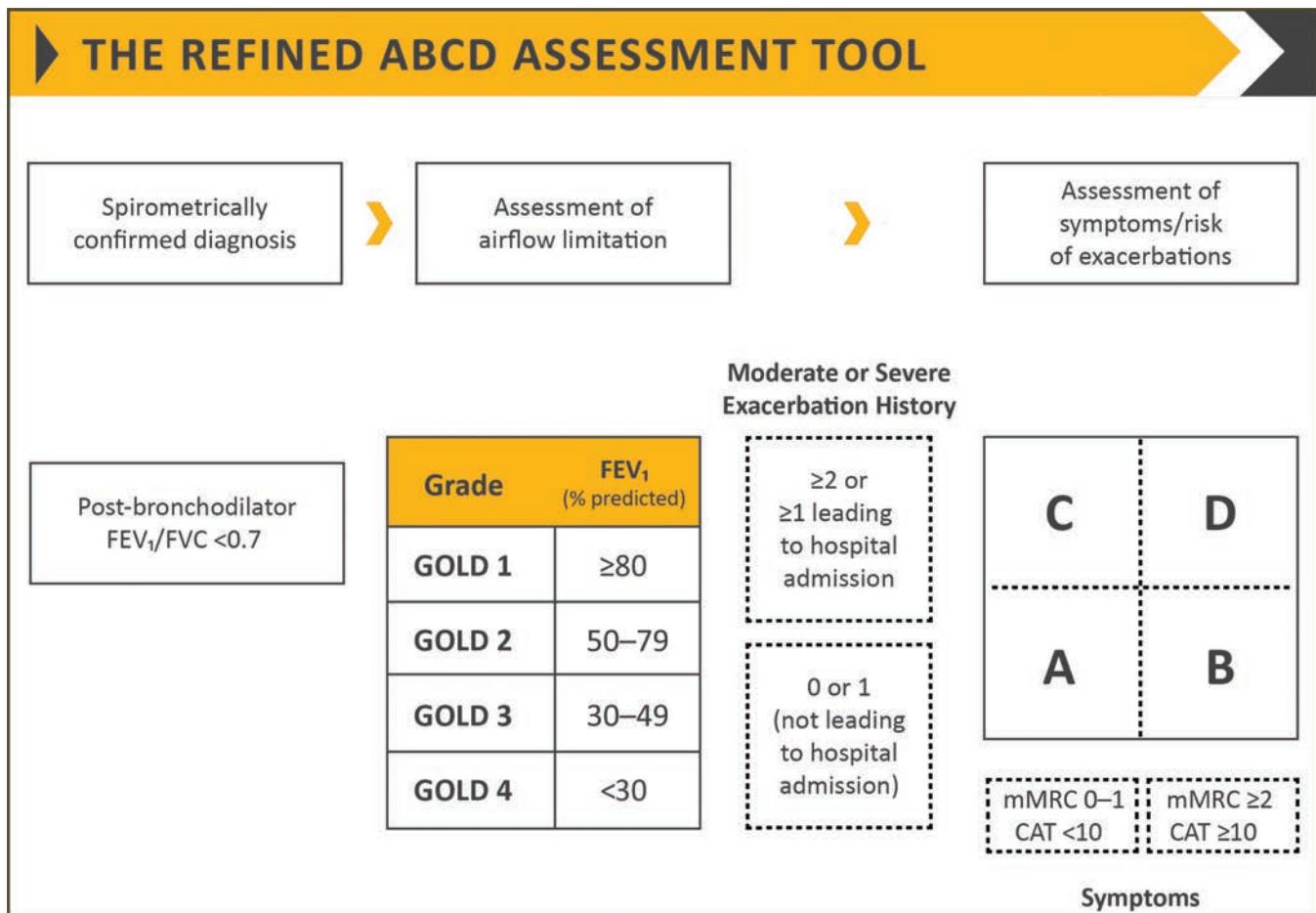


Figure 38-1 COPD Assessment tool from GOLD guidelines highlights the importance of consideration of symptoms and exacerbation frequency in assessing COPD severity. (Reproduced with permission from

Pocket Guide to COPD Diagnosis, Management, and Prevention. A Guide for Health Care Professionals. 2020 Global Initiative for Chronic Obstructive Lung Disease.)

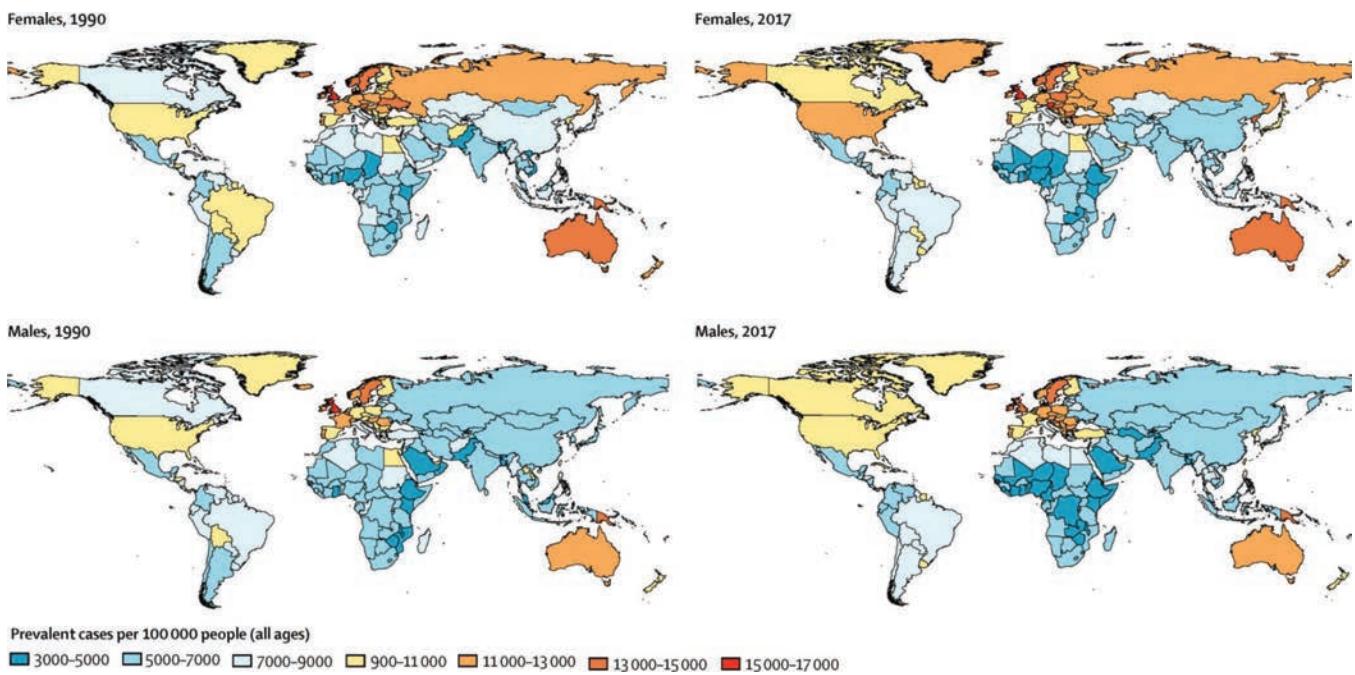


Figure 38-2 There has been a significant increase in the burden of chronic respiratory disease with 544.9 million people affected, a 39.8% increase in prevalence from 1990 to 2017. (Reproduced with permission from Soriano JB, Kendrick PJ, Paulson KR, et al. Prevalence and

attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Respiratory Medicine*. 2020;8(6):585–596.)

further about risk stratification. There is increasing evidence that current and former smokers can have parenchymal and airway abnormalities and can have respiratory symptoms and exacerbation-like events, even in the absence of airflow limitation. At present, these patients are not included in COPD management guidelines.^{1,8,9}

EPIDEMIOLOGY

COPD is a significant health problem affecting more than 400 million people worldwide. In 1990, COPD was the sixth most common cause of disease worldwide but now ranks as the third leading cause of death, according to the Global Burden of Disease Study, after cardiovascular disease and stroke.¹⁰ The impact of respiratory diseases, and specifically COPD, is wide-reaching as it affects countries at all levels of development (Fig. 38-2). The World Economic Forum estimates that the global costs of COPD will reach U.S. \$50 trillion annually by 2030.¹¹

Often viewed as a self-inflicted disease of tobacco smokers, the paradigm is shifting with an increased understanding of the disease. Fletcher and colleagues in the 1960s showed increased lung function decline in susceptible smokers and that smoking cessation would decelerate the decline of lung function.¹² Smoking remains prevalent worldwide, and while smoking is decreasing in developed nations, the global burden of disease continues to grow (Figs. 38-2 and 38-3).^{13,14} Reasons for the increasing global burden of disease include an increasing burden of tobacco smoke exposure in low to middle-income countries, persistent problems with preterm birth, poor nutrition and childhood infections, toxic nontobacco exposures, and an expanding number of older adults.^{15–18} Exposure to indoor and outdoor pollution from the combustion of clean fuels (gas stoves and burning petroleum) and unclean fuels (coal, charcoal, wood, or dung) plays a significant role in developing COPD in never smokers.^{19–21} In areas where indoor air pollution is generated by burning biomass for heating and cooking, COPD disproportionately affects women and children.^{22,23}

COPD has a high prevalence and poses a significant burden with astounding morbidity, mortality, and financial and social impact.

Surveys, such as the 2017 Behavioral Risk Factor Surveillance System (BRFSS), suggest that an estimated 15 million people in the United States have COPD. The estimated worldwide prevalence ranges from 7% to 19%. Despite its wide-reaching effects, current data underestimate the burden of disease as it is underrecognized and underdiagnosed.^{24–28} In the United States, the age-adjusted prevalence of COPD was 6.2%, with a higher prevalence among the less educated, lower socioeconomic status, rural communities, women, older adults, and American Indians/Alaska Natives.²⁶ Other statistics support these national surveys. In a study of 1575 cigarette smokers, aged 30 or older, with a 10 or more pack-year smoking history, approximately 20% met spirometric criteria for COPD.²⁹ The Third National Health and Nutrition Examination Survey (NHANES III) showed that life expectancy is shortened by 5.8 years for men aged 65 with GOLD stage 4 COPD, and an additional 3.5 years if smoking is continued.³⁰ With the growing impact of COPD, there is an urgent need for primary prevention efforts and improved recognition and management of this deadly disease.

ETIOLOGY

Risk factors for COPD development are environmental and host-based (Table 38-1, Fig. 38-4). Throughout the human lifespan, several host factors have unique and dynamic interactions with the environment that mediate one's likelihood of disease.³¹ These host factors include the balance of mechanisms responsible for tissue maintenance, tissue repair, tissue regeneration, and the mechanisms associated with tissue damage and aging.³² The interaction of host and environmental factors determines the likelihood of activating the cellular and biochemical mechanisms responsible for developing COPD. In developed countries, smoking tobacco is the predominant risk factor; however, never-smokers also develop COPD, and women predominate in this cohort.^{16,33} In places where solid fuels are burned, indoor air pollution is a dominant risk factor. Other factors associated with COPD include second-hand tobacco exposure, a family history of COPD, age, socioeconomic status, education level, history of tuberculosis, prematurity, in utero

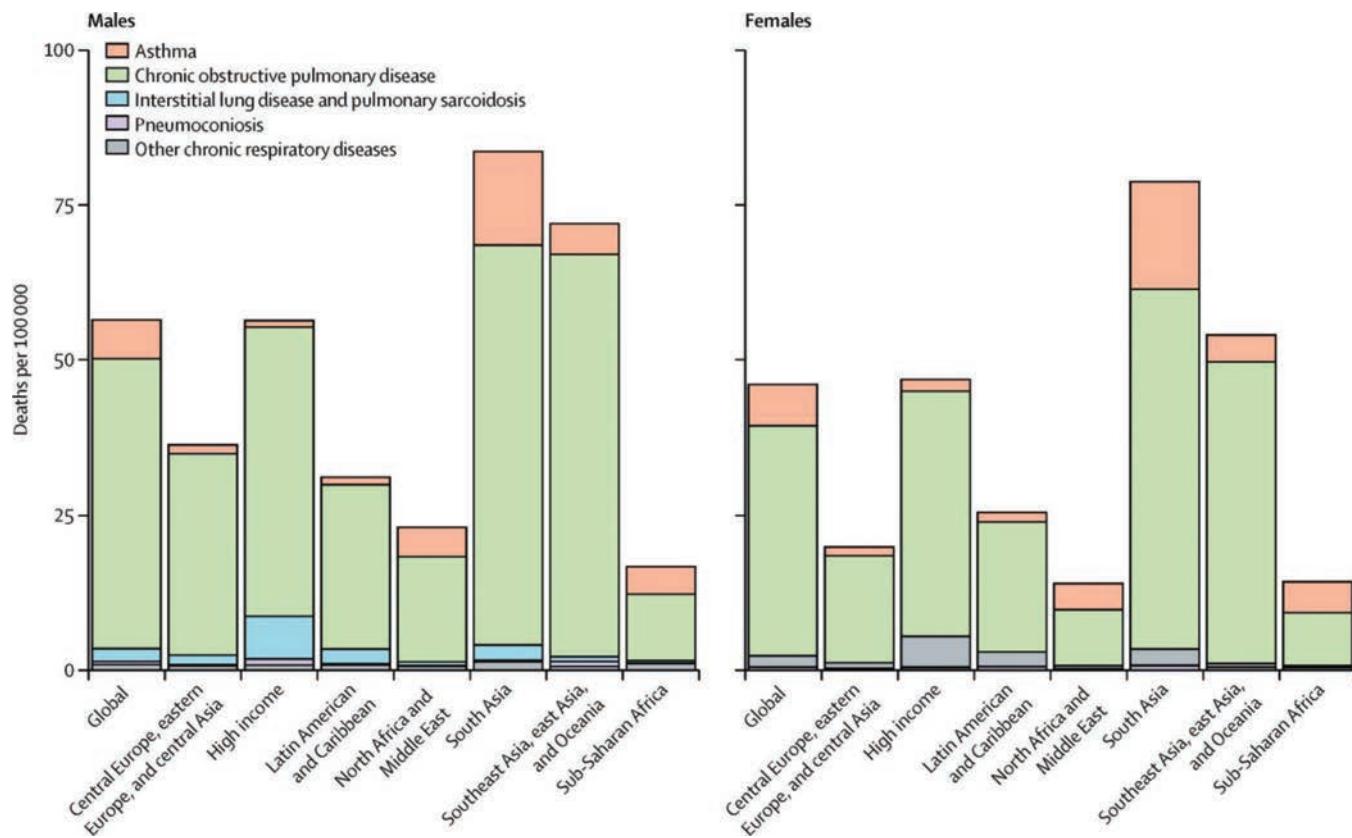


Figure 38-3 COPD accounts for the majority of respiratory disease-related mortality globally, for all ages, and in all regions of the world. (Reproduced with permission from GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585–596.)

exposures, hospitalizations for respiratory illness in early childhood, and occupational exposures.³⁴ Multiple risk factors may be present in a single individual.

Environmental

Environmental exposures include tobacco exposure, indoor pollution, occupational exposures, geography, and socioeconomic status, impacting the disease's regional burden.

Smoking

Worldwide, between 20% and 40% of all COPD patients are never-smokers.³³ This ratio is not the same in developed countries where tobacco smoke-related COPD accounts for approximately 80%.³⁵ In the United States, there is an overlap between smokers' geographic distribution and the geographic distribution of individuals with COPD. Although the relationship between COPD and tobacco smoke exposure is not linear, there is a correlation between overall lung health, including airflow obstruction based on FEV₁ and duration of tobacco smoke exposures. Traditionally reported as pack-years smoking, there is a growing body of evidence showing that

monitoring smoking duration is more sensitive and reliable because it is more precise and not as affected by reporting and recall bias.^{36–38} Tobacco smoke exposure early in childhood is even more critical as it results in stunted lung maturation. By middle age, the rate of lung function deterioration with continued tobacco smoke in children with early tobacco smoke exposure outpaces that of former smokers and never-smokers.^{39–41}

There may be other unrecognized environmental factors. For poorly understood reasons, women have more lung function reduction with early onset of COPD with lower total exposure and a higher proportion of never-smokers with COPD.^{42,43} Some data indicate racial disparities in the risk of developing COPD, with African Americans showing similar severity of COPD to whites with fewer pack-years of smoking.^{25,44,45} While a decline in FEV₁ is not inevitable in all smokers, those with sustained reductions in FEV₁ and continued smoking have more adverse effects on ventilatory function.^{37,46–48}

Environmental Tobacco Smoke Exposure

Human exposure to environmental tobacco smoke (ETS) is associated with an increased incidence of pulmonary and cardiovascular disease and is a possible risk for carcinogenesis.^{49–51} ETS is implicated in the loss of many years of the life of adults and children in the United States, with observable sociodemographic disparities.⁵² Controlled experimental studies with healthy volunteers indicate that short-term exposures to ETS levels comparable to those in real-life situations affect serum cytokine levels and pulmonary function and, if recurrent or chronic, might translate into COPD.^{17,53} In utero effects of maternal smoking on lung growth and subsequent risk of childhood wheezing, asthma, and lung diseases in adulthood are evident.^{41,54} The association between ETS and COPD is not a direct

TABLE 38-1 Risk Factors for COPD

| Environmental | Host-based |
|--------------------------|------------------------|
| Smoking | Genetic |
| Indoor air pollution | Airway hyperreactivity |
| Occupation | |
| Low socioeconomic status | |

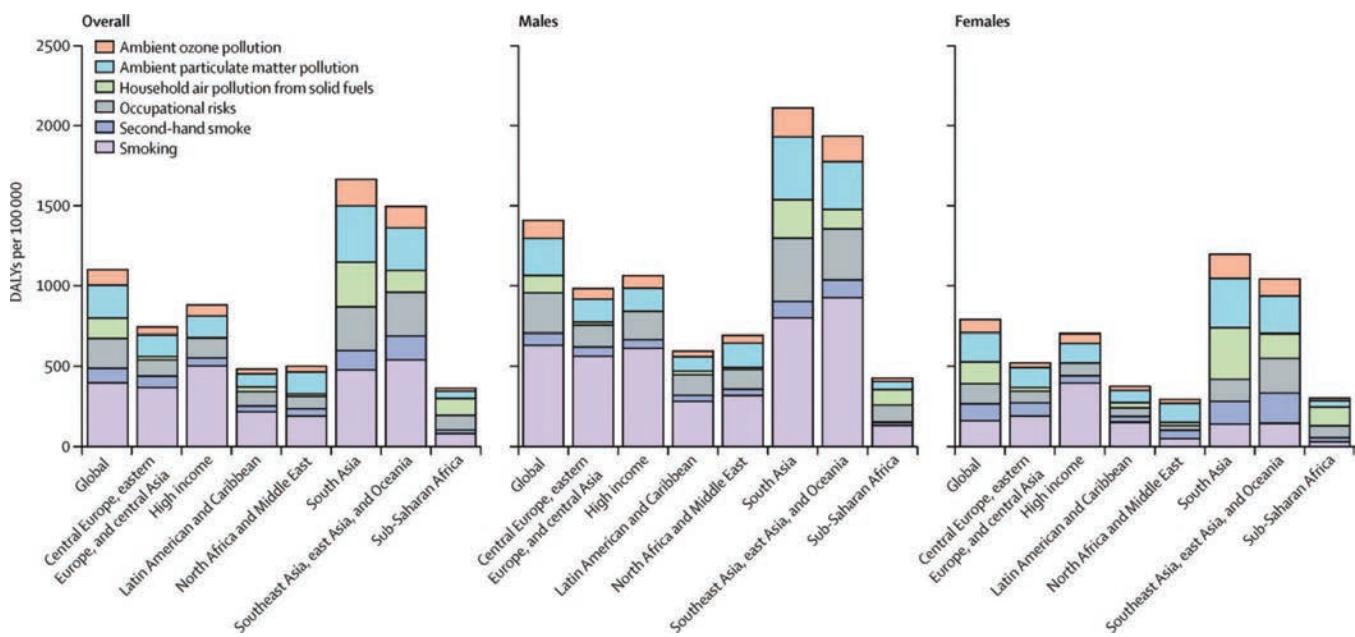


Figure 38-4 The impact of tobacco smoke exposure remains large; however, the effect of non-tobacco exposures is substantial as represented by attributable disability-adjusted life year (DALYs) rates for each risk factor across regions in 2017. (Reproduced with permission

from GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med.* 2020;8(6):585–596.)

association; however, the effect of ETS in early childhood results in alteration and limitations in the maximally attained lung function, and in some, it adversely impacts the rate of decline, thus contributing to increased COPD risk.^{41,55} Like chronic smoking and occupational exposures, ETS is an independent risk factor for developing chronic lung disease, so avoidance is recommended.

Air Pollution

Long-term exposure to air pollution increases COPD risk and increases the symptom burden for those with respiratory and allergic illnesses.⁵⁶ These adverse effects on the respiratory system are observed even with very low air pollution levels, below national standards for acceptability.^{20,57} The effects of outdoor air pollution are well established; however, a growing body of evidence has shown that indoor air pollution is a significant health concern. Sources include burning solid fuels such as wood and animal dung for cooking and heating. This practice is widespread in parts of the world and disproportionately exposes women and children to high smoke concentrations containing respirable particles. These complex gas mixtures are often inhaled for many hours daily. Cough and sputum often occur among those exposed to indoor air, with decreased bronchitic symptoms coincident with measures that reduce smoke levels.^{19,58} The World Health Organization estimates that more than one million people a year die of COPD precipitated by indoor air pollution, so international advocacy organizations are working diligently to curb its impact.^{59,60}

Occupation-Related Exposures

Many studies have assessed the relationship between COPD outcomes and occupational exposures, and about 15% of COPD cases are attributed to occupational exposures, even after accounting for tobacco smoke exposures.⁶¹ The possibility that occupation-related inhalation of particulates and gases carries a risk for COPD was slow in gaining acceptance, but acceptance is widespread now.^{62,63}

Prolonged exposure to a range of substances has the potential to cause COPD. The majority of available information on occupational

exposures has focused on a few substances and industries. Most data available focuses on exposure to dust and fumes and less so on other airborne pollutants such as gas, fumes, and vapors.⁶⁴ Challenges to quantify the burden of disease related to occupational exposures include the difficulty that results from workplace heterogeneity. Most risk assessment tools do not accurately adjust for the variability in exposures based on the workplaces, country, or evolution of workplace hazards over time.^{65,66} Agents that increase risk include but are not limited to dust from cadmium, grain, flour silica, minerals and other organic dusts, cadmium fumes, welding fumes, and wood ash.^{67,68} In addition to the well-recognized risk of occupations involving exposure to organic and inorganic dusts, other less “risky” occupations, such as construction, plastics manufacturing, and utility work, may carry an increased risk of COPD.^{69,70} The risk of adverse occupational exposure is particularly crucial in workers who smoke or have other host-based factors that raise their risk for COPD, such as genetic variants including $\alpha 1$ -antitrypsin deficiency.⁷¹ Occupational risks are modifiable and provide a unique opportunity for disease prevention.

Social Determinants of Health

Socioeconomic status plays a significant role in health outcomes. Like in many other chronic illnesses, health disparities exist in COPD-related health outcomes. Rural residence, low socioeconomic status, and potentially ancestry are identified as risk factors for COPD in the United States and other countries worldwide.^{72–75} The relationship is linked to increased tobacco exposure and exposure at earlier times in life, low birth weight, respiratory infections in early childhood, limited access to medical care, rates of HIV and tuberculosis, occupational exposure to inhaled particulates, and increased exposure to household allergens.

In the United States in 2011, 45% of adults with a General Education Diploma (GED) were smokers compared to 10% of individuals with a college degree, and for adults living below the poverty level, 33% were smokers in contrast to 20% of individuals living above the poverty level.⁷⁶ Focused efforts at addressing factors that

reduce health disparities have proved effective in many diseases and may impact the burden of COPD.

■ Infections

COPD is characterized by chronic inflammation, and while the host-pathogen interaction is not fully understood, the role of chronic and frequent infection in the pathogenesis of COPD is an area of research. Several pathogens, such as HIV and tuberculosis, have been associated with increased COPD risk. Furthermore, lower respiratory infections in childhood have been shown to affect lung health in adulthood adversely.

Tuberculosis

Tuberculosis (TB) is the most common infectious cause of death worldwide, with an estimated 1.3 million deaths in 2019. Pulmonary TB is the most common form of the disease and is associated with significant chronic pulmonary sequelae, even despite microbiologic cure.⁷⁷ Tuberculosis is a significant risk factor for COPD; however, the mechanism remains unclear and whether the airflow obstruction is from scarring and other postfibrotic changes.^{78,79}

Human Immunodeficiency Virus (HIV) Infection

First identified in 1989, HIV-associated COPD has a reported prevalence of between 6% and 15%.^{80,81} Individuals with HIV who smoke have an increased risk of COPD with a propensity toward emphysema development.^{82–84} The risk is modulated by increased oxidative stress, systemic inflammation with chronic immune activation, and endothelial dysfunction.^{81,85–87} It is unclear if these mechanisms are a direct alteration due to HIV infection or a downstream response to alteration of innate immune responses. COPD and pulmonary hypertension in smokers with HIV appear to be more common in individuals with a high viral load and lower CD4 cell counts and not an adverse consequence of antiretroviral therapy.^{88,89} Despite the association of HIV disease control and adverse COPD outcomes, emphysema seen in HIV patients is not reversible in relation to viral load or recovery of CD4 cell counts.

Childhood Lower Respiratory Tract Infections

The complex interaction of host-based factors and environmental predisposition to disease is of particular significance in childhood. In utero events and exposures, early childhood infections, and other events impact peak lung function. Stunted lung maturation increases the risk of developing lung diseases such as COPD later in life.⁴¹ Continued smokers experience further declines in FEV₁ in adulthood.³¹ Since the status of lung function in very early childhood predicts ventilatory function many years later, it is essential to promote overall lung health. This can be done by efforts to minimize exposure to allergens, decreasing tobacco exposure, and optimizing access to healthcare and management of respiratory diseases.⁹⁰

Genetic Factors

There is marked variability in COPD development among smokers, with an estimated 10% to 15% of smokers developing clinically significant disease. Genetic variation has significant effects on COPD susceptibility, and heritability estimates for COPD range from 37% to 50%.^{91–93} A complex genetic disorder, COPD is caused by the interaction of multiple genes and the environment. Endotypes of COPD are when a known molecular mechanism results in observable disease such as seen in telomerase reverse transcriptase (TERT) gene polymorphisms that affect the action of telomerase and mutations that result in α 1-antitrypsin deficiency. Alpha-1-antitrypsin deficiency is autosomal recessive and the most apparent genetic link to COPD.

Alpha-1 Antitrypsin Deficiency Laurell and Erikson in 1963 identified that a deficiency in the neutrophil elastase inhibitor α 1-antitrypsin (α 1-AT) was associated with COPD.⁹⁴ Genetic variants in *SERPINA1* (serpin peptidase inhibitor, clade A, member 1) are responsible for α 1-AT. Genetic variants in *SERPINA1* result in an imbalance between α 1-AT and neutrophil elastase, increasing the risk of emphysema. Most of the mutations in the 12.2-kb gene that encodes α 1-AT are single nucleotide polymorphisms (SNPs) with letters specifying the allelic variants. The original letters were chosen to reflect electrophoretic mobility: F = fast, M = medium, S = slow, and Z = ultraslow (Fig. 38-5). Homozygosity for the M allele, Pi MM, is present in about 95% of adults in the United States. Homozygotes for the Z allele (ZZ), S allele (SS), and compound heterozygotes (ZS) have lower serum α 1-AT levels and an increased risk for COPD and emphysema.^{95–97} The relationship of heterozygosity to COPD risk had been controversial, but it is increasingly evident that Pi MZ individuals have more airflow impairment, as measured by FEV₁/FVC and more emphysema on CT scans than matched Pi MM individuals.^{98,99} Even after accounting for the genetic variants in *SERPINA1* and the strong association with COPD, there remains unexplained variability in COPD risk.^{100,101}

Telomerase Polymorphisms Deleterious mutations in the telomerase reverse transcriptase gene (TERT) affect the stability and processing of the enzyme.¹⁰² TERT mutations are associated with aging effects that increase COPD susceptibility.¹⁰³ Telomeres are DNA-protein structures located at the end of the chromosome and

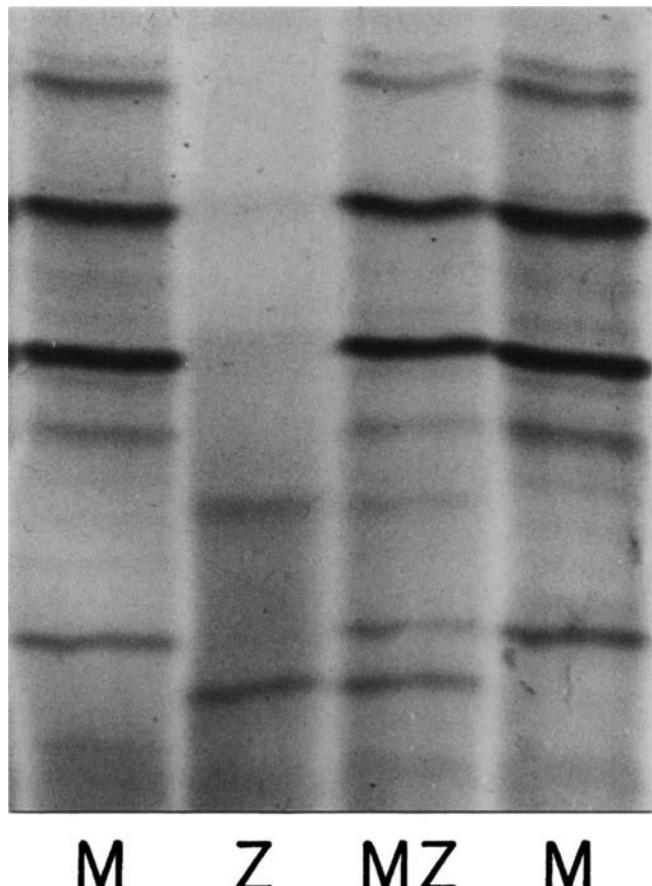


Figure 38-5 Patterns of Pi M, Pi Z, and Pi MZ α 1-AT on isoelectric focus. By this analysis, α 1-AT has microheterogeneity and thus appears as multiple bands. Pi M and Pi Z have distinctly different band patterns, while Pi MZ has a pattern that combines both Pi M and Pi Z. (Reproduced with permission from John A. Pierce, M.D.)

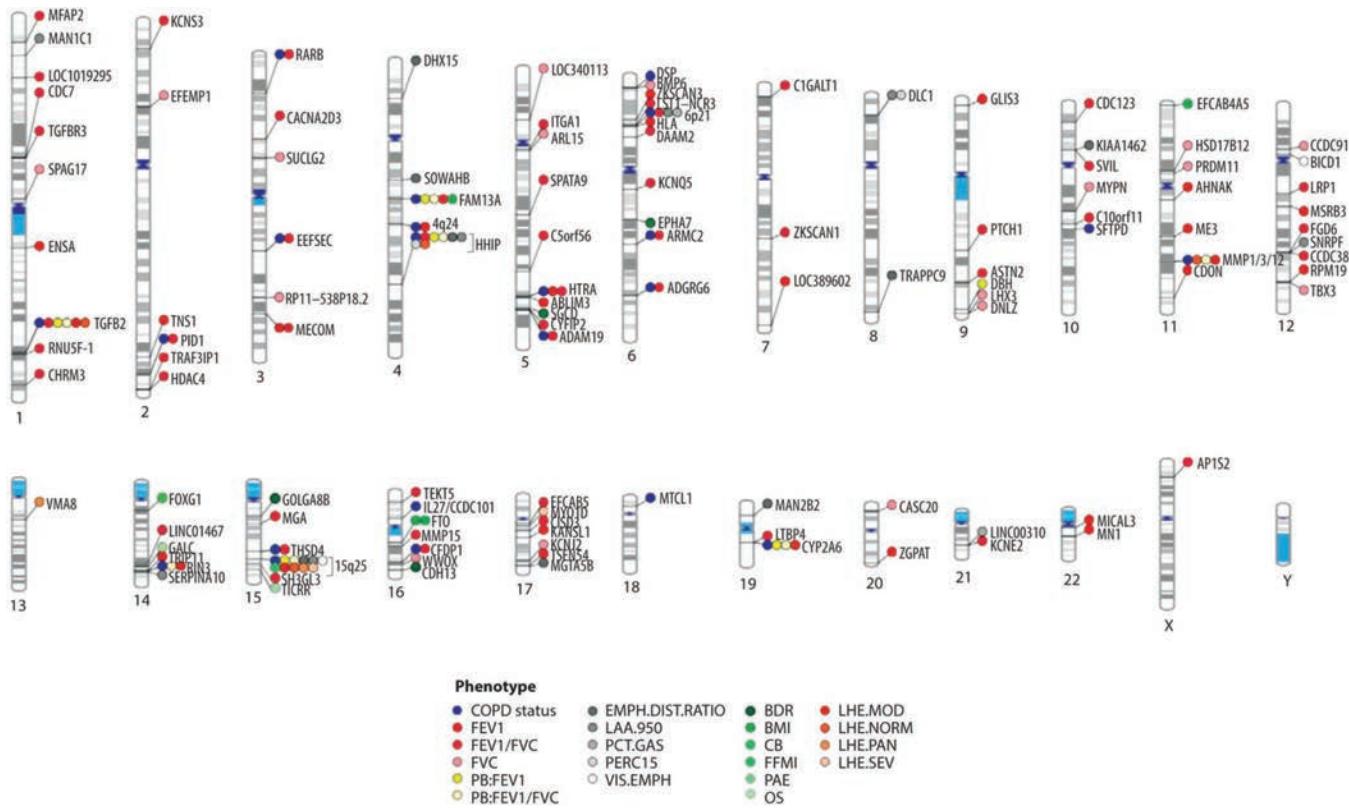


Figure 38-6 Genetic Determinants of COPD-related phenotypes. Phenogram plot of representative genetic associations of GWAS for COPD. Associations are nearest gene to the associated SNP. COPD susceptibility associations (blue), lung function associations (red). BDR, bronchodilator response; BMI, body mass index; CB, chronic bronchitis; EMPH.DIST.RATIO, emphysema distribution ratio of upper divided by lower lung fields; FEV1, forced expiratory volume in 1 s; FFMI, fat-free mass index; FVC, forced vital capacity; GWAS, genome-wide association study; LAA.950, percentage of lung density histogram below –950 HU; LHE, local histogram-based emphysema; MOD, moderate centrilobular

emphysema on LHE; NORM, normal/nonemphysematous on LHE; OS, resting oxygen saturation; PAE, pulmonary artery enlargement; PAN, pan lobular emphysema on LHE; PB, postbronchodilator; PCT.GAS, percent gas-trapping at –856 HU on expiratory computed tomography; PERC15, fifteenth percentile point of the lung density histogram; SEV, severe centrilobular emphysema on LHE; SNP, single nucleotide polymorphism; VIS.EMPH, visual emphysema (presence/absence). (Reproduced with permission from Ragland MF, Benway CJ, Lutz SM, et al. Genetic Advances in Chronic Obstructive Pulmonary Disease. Insights from COPDGene. Am J Respir Crit Care Med. 2019;200(6):677–690.)

are responsible for protecting the chromosome's integrity throughout the cell cycle. Telomeres gradually shorten with cell division and maturation, and when they reach a certain threshold, they result in cell senescence and apoptosis.¹⁰⁴ TERT polymorphisms disproportionately affect women, increase the pneumothorax risk, and are associated with early-onset emphysema in smokers.¹⁰⁵ They are seen in approximately 1% of COPD patients and are described in familial idiopathic pulmonary fibrosis.¹⁰⁶ TERT polymorphisms highlight that small changes combined with exposures such as tobacco smoke and air pollutants contribute to increased susceptibility.¹⁰⁷

Other Genetic Variants Efforts to identify other genetic loci are ongoing in multiple cohorts. The Framingham Heart Study cohort was the first genome-wide association study (GWAS) to assess lung function. In this cohort, a variant in interleukin 6 receptor (IL6R) and glutathione-S-transferase omega-2 (GSTO2) were associated with the degree of airflow obstruction.¹⁰⁸ COPD is heterogeneous, and mutations in several disease pathways have been associated with COPD risk and outcomes (Figs. 38-6 and 38-7). The inflammatory pathways (IL6, IL6R), protease imbalance (SERPINA1), oxidant stress (GSTO2), nicotine metabolism, and dependence (cytochrome P-450 2A6) are just a few pathways with disease-associated genetic variants.^{108–112} The cholinergic nicotinic acetylcholine receptor exemplifies COPD's genetic complexity. Several mutations in this pathway, including HHIP and CHRNA3/5, have been associated

with COPD risk; further, several factors, including epigenetic factors, mediate the expression and subsequent disease associations. The CHRNA3/5 locus is associated with increased smoking intensity and emphysema while the HHIP locus with COPD exacerbation frequency.¹¹³

Given the polygenic pathogenesis, polygenic risk scores have been shown to increase the predictive power for COPD, and this has the potential to identify susceptible individuals at an earlier age.^{114–116}

PATHOPHYSIOLOGY

COPD represents the clinical expression of complex alterations in the structure and function of alveolar tissue and small airways. Many processes at the tissue and cellular levels can be implicated, including inflammation, cell proliferation, apoptosis, the altered phenotype of lung cells, and remodeling of the extracellular matrix. Numerous mediators, most notably proteinases, oxidants, and cytokines, are involved in these processes mediate the observable physiology in COPD.

Hogg and colleagues observed that airways 2 mm or less in internal diameter typically contribute only a minor part of the total airway resistance, but these airways are the principal sites of increased airway resistance in COPD.¹¹⁷ The physical basis for small airway resistance in COPD has been considered a combined result of emphysema causing minor airway instability and collapse along

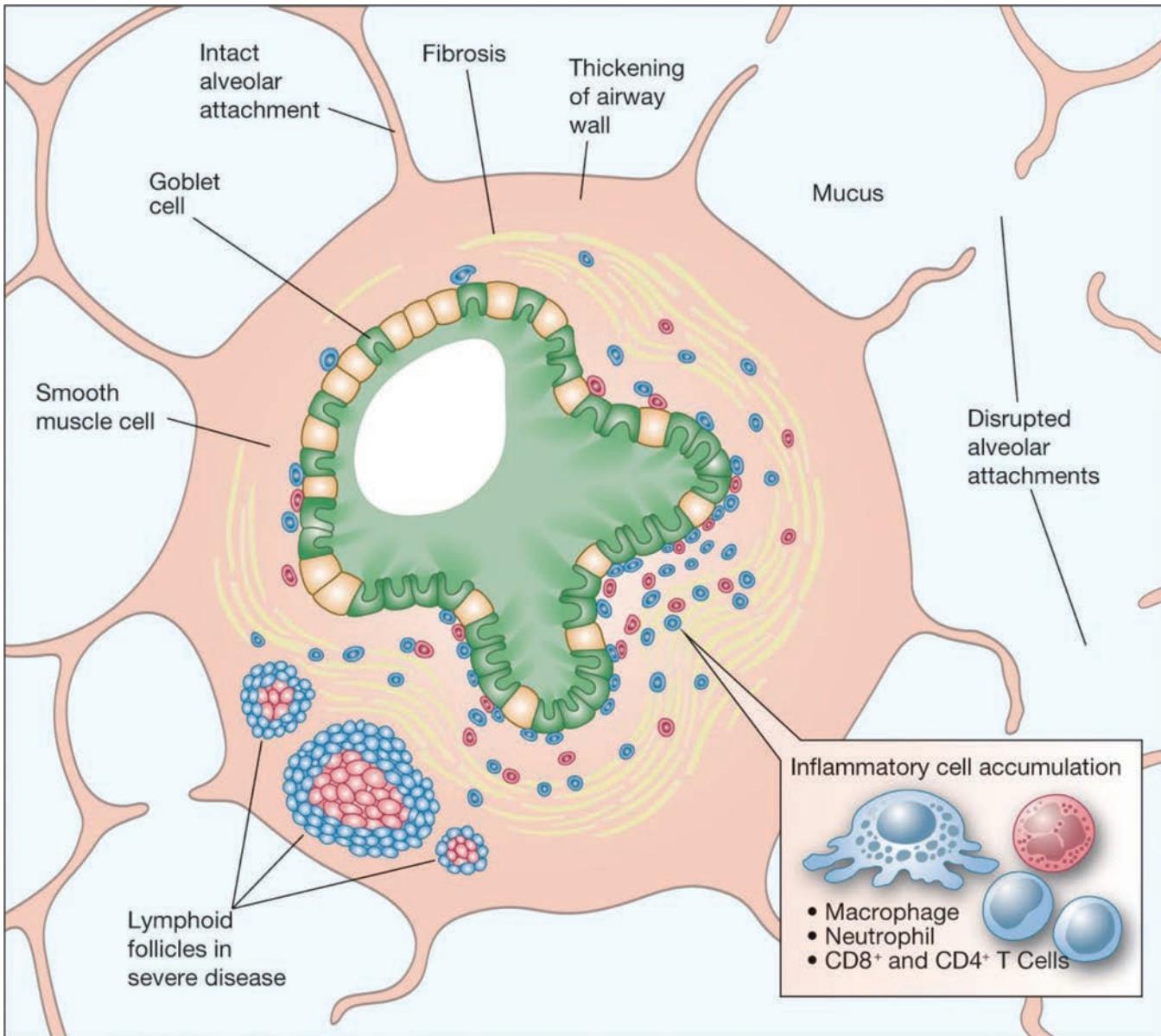


Figure 38-7 The differences in lung function decline exemplify heterogeneity of COPD outcomes. Histogram of the mean annual FEV₁ decline (L) for 751 patients with COPD followed for a median of 64 months and up to 10 years, with an average of 5.44 annual measurements (stratified by ATS/ERS and GOLD severity classification as follows:

32 [4%] mild [FEV₁% ≥80]; 256 [34%] moderate [FEV₁% 50–79]; 245 [33%] severe [FEV₁% 30–49]; and 218 [29%] very severe [FEV₁% <30]. (Reproduced with permission from Nabel EG: ACP Medicine: Pulmonary, Hamilton, Ontario, Canada: Decker Publishing; 2011.)

with multiple anatomic abnormalities narrowing the lumens of small airways. Because emphysema and small airway pathology are common in individuals with COPD, their relative contributions to airflow obstruction have been difficult to discern.

A fixed reduction in airflow is associated with several specific pathologic findings in the small airways of advanced COPD (Fig. 38-8). Small airways in the lungs of individuals with COPD typically show goblet cell metaplasia, replacement of Clara cells with mucus-secreting cells, and infiltration of the airway walls by inflammatory cells that, in severe disease, include an increased surface area of lymphoid follicles.¹¹⁸ The cellular changes are accompanied by increased connective tissue in the subepithelial and adventitial compartments of the airway walls.¹¹⁸ Alveolar tissue surrounding small airways usually provides radial traction on bronchioles at points where alveolar septa attach. Loss of these bronchiolar attachments

resulting from proteolytic destruction may contribute to airway distortion, narrowing, and instability.

Advances in CT image analysis techniques, such as parametric response mapping (PRM), have identified earlier, more predictive manifestations of disease to analyze emphysema pattern and location, measures of airway caliber such as degree of expiratory central airway collapse, and distal airway dropout, among others.^{119–122} The large-scale pathologic loss of terminal airways in advanced disease contributes significantly to the small airway resistance. It is unclear if the radiographic loss of small airway surface area in early disease is pathologic destruction, severe wall thickening, or mucus plugging that obscures the lumen below the radiographic resolution. However, more severe airflow obstruction is associated with increases in the thickness of all components of the airway wall.¹²⁰ The most significant relative increase in the airway wall components is in the

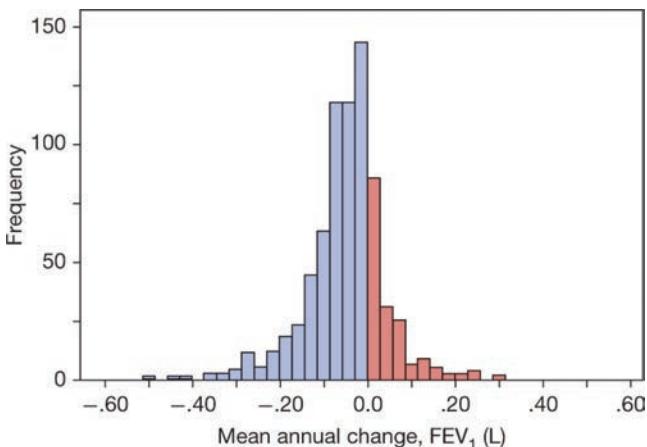


Figure 38-8 Pathologic lesions in small airways in COPD. Multiple abnormalities lead to partial obstruction of the lumen and altered shape and mechanical properties of the airways. (Reproduced with permission from Casanova C, de Torres JP, Aguirre-Jaime A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. *Am J Respir Crit Care Med.* 2011;184(9):1015–1021.)

connective tissue-rich adventitial layer. The epithelial layer, the lamina propria, and the smooth muscle-containing layer all demonstrate significant increases in advanced disease, and small airway mucus plugs have been significantly associated with airflow limitation in severe disease.¹²³ The interplay of small airway pathology, radiologic loss of small airways, emphysema, and their role in causing the airflow obstruction in early COPD are ongoing research areas.

Airflow Obstruction

The American Thoracic Society (ATS) and GOLD recommend utilizing post-bronchodilator FEV₁/FVC less than 0.70 as the threshold for the detection of airflow obstruction. Defining and appropriately classifying persons with a reduced FEV₁ with a normal FEV₁/FVC and normal TLC has been controversial. These patients are defined as preserved ratio impaired spirometry (PRISm), an entity that some suggest should not be classified as COPD or interpreted as an obstructive ventilatory defect, while others argue that it should, given the similarity in pathogenesis and similar outcomes such as mortality when compared with COPD.^{124,125}

The FEV₁ is an important marker of airflow and it reflects the balance between the elastic recoil of the lungs promoting expiratory flow and the resistance of the airways limiting flow during the performance of an FVC. In normal lungs and lungs affected by COPD, maximal expiratory flow diminishes as the lungs empty because the lung parenchyma provides progressively less elastic recoil, and the cross-sectional area of the airways falls. This leads to an increase in airway resistance. The decrease in flow coincident with the decrease in lung volume is apparent on the expiratory limb of the flow-volume curve (Fig. 38-9). In mild COPD, the abnormality in airflow is evident only at lung volumes at or below functional residual capacity, appearing as a “scooped out” lower part of the descending limb of the flow-volume curve. In many patients with advanced COPD, the entire curve demonstrates decreased expiratory flow. There is wide variability in COPD in the relationships among FEV₁, exercise tolerance, alveolar gas exchange, and quality of life.¹²⁶ The correlation between FEV₁ and small airway pathology is strong, and it likely contributes to the reduction independent of the correlation of FEV₁ with emphysema.

Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) is present when there is an acute, temporary decline in maximal expiratory airflow in

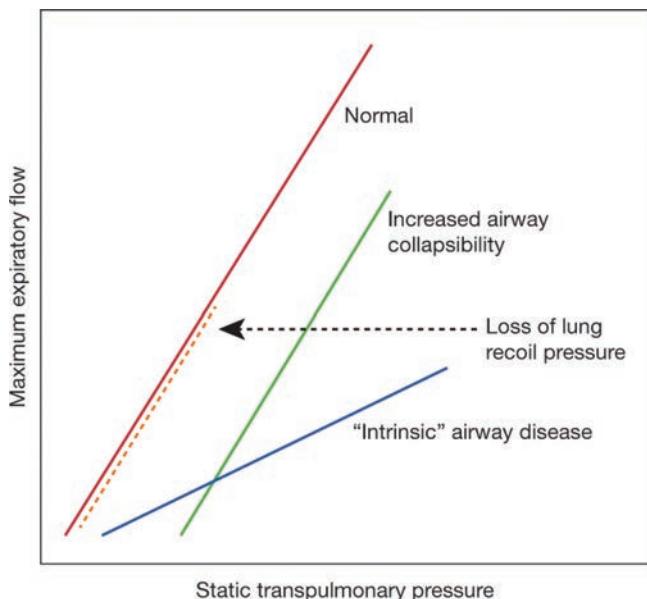


Figure 38-9 Reduced maximum expiratory flow in COPD from maximum expiratory flow versus lung recoil pressure curves. Loss of lung recoil, emphysema (heavy interrupted line)—the flow-pressure curve slope remains normal, but the curve terminates at a lower pressure than normal. Due to airway obstruction, the slope is reduced. Increased airway collapsibility, due to decreased elastic recoil, causes displace the curve to the right. In COPD, the flow-pressure curve has premature termination and a decreased slope and is shifted rightward, indicating decreased elastic recoil, increased airway resistance, and increased airway collapsibility are all involved in the reduced maximum expiratory flow. (Reproduced with permission from Calverley PMA, Pride NB. *Chronic Obstructive Pulmonary Disease*. London, Chapman & Hall; 1995.)

response to inhaling potential bronchoconstricting agents such as methacholine or histamine. Historically the “Dutch hypothesis” postulated that asthma and COPD are two different manifestations of the same disease due to the similarity in features such as the presence of airway hyperresponsiveness.¹²⁷ Distinct from asthma, the type and cause of airway inflammation and consequences of the inflammatory process are different in COPD. Smokers typically do not show AHR until their FEV₁ is reduced, and experimental induction of emphysema often leads to AHR.¹²⁸ AHR is of clinical significance as it is associated with an accelerated decline of FEV₁ and is a negative prognostic marker.¹²⁹ In the Lung Health Study, AHR was second to smoking as an essential determinant of decline in FEV₁, and it was not related to the initial level of obstruction. AHR was more significant in women smokers than men smokers.¹²⁹ Although AHR decreased after smoking cessation and bronchodilator responsiveness improved, bronchodilator responsiveness did not correlate with the rate of FEV₁ decline.¹³⁰

An important component of COPD, AHR in individuals with COPD is underestimated due to the infrequency of bronchoprovocation testing in patients with COPD. It may be a consequence of emphysema, airway wall stiffness, and parenchymal tethering by the extracellular matrix.¹²⁸ Distinctions in airway hyperresponsiveness in COPD and asthma are still a significant topic of interest.¹²⁸

PATHOGENIC MECHANISMS

Numerous well-established pathogenic mechanisms result in the observable COPD phenotypes. These mechanisms include

dysregulated inflammatory reactions, excess oxidant stress, mucus hypersecretion, and proteinase imbalance resulting in elastic fiber degradation and increased collagen turnover.

■ Inflammation

Inflammatory responses can be divided into innate and acquired types.

Innate Immune Responses

Tobacco smoking and other inhaled irritants lead to the recruitment, infiltration, and activation of innate inflammatory cells in the lungs and airways, where an excess of the products of these cells injure lung tissue and disrupt lung repair mechanisms.^{118,131,132} Some inflammatory cell types important in COPD include neutrophils, macrophages, and variably eosinophils, but also dendritic cells and lymphocytes. The increased presence of airway inflammation is demonstrated by inflammatory cells in lung biopsy specimens, bronchoalveolar lavage fluid, and sputum as well as increased volatile products of inflammation in exhaled breath.^{133–137} While the presence of inflammatory change can be a normal response to oxidative stress and tissue damage due to irritants such as cigarette smoke, maladaptation of these integral functions to the innate immune dysfunction is key in COPD pathogenesis. Once COPD is established, there can be continued oxidative stress and progression from endogenous sources such as mitochondrial respiration even after the cessation of inhaled toxic exposures.¹³⁸

Activated macrophages and neutrophils are the major participants in lung inflammation in COPD.¹³⁹ Monocytes become alveolar macrophages after migrating into the lungs by sensing and following chemoattractant gradients of cytokines and bacterial peptides produced by tissues of infection or inflammation.^{140,141} Essential to establishing homeostasis of the inflammatory milieu, alveolar macrophages have both anti-inflammatory (M1) and inflammatory (M2) phenotypes. COPD patients have a dominant M2 phenotype, with several alterations that result in defective phagocytosis and changes in abnormal secretion of cytokines and chemokines.^{142–144} Alveolar macrophages in COPD release proteinases that degrade the extracellular matrix of the lung and release chemotactic factors that recruit other inflammatory cells to the lungs.¹⁴⁵ Unlike most circulating cells such as neutrophils that decrease within weeks of limited tobacco smoke exposure, activated alveolar macrophages may be present even years after smoking cessation.^{146,147}

Neutrophilic inflammation induced by byproducts of cigarette smoke, viruses, bacteria, and oxidative stress is characteristic of COPD and is the predominant mediator of mucus hypersecretion.^{148,149} Neutrophilic inflammation in COPD is unfortunately not responsive to available therapies, with minimal response to steroid therapy.^{148,150} Airway epithelial cell exposure to pollutants and inflammatory peptides activates the production of neutrophilic mediators and chemoattractants such as CXCL1, CXCL8, and leukotriene B₄, engaging chemoreceptors CXCR2 and BLT1 receptors.¹⁵¹ All of these are produced in excess in patients with COPD. Investigations into therapeutics such as CXCL8 blockade or the signaling cascade intermediaries such as TNF- α and IL-1 β have not shown benefit in lung function or frequency of exacerbations.^{148,150,152} Macrophages and neutrophils are commonly seen in patients with COPD; however, the role of eosinophils is now increasingly understood.

The role of eosinophilic inflammation has garnered a lot of attention. About 20% to 40% of patients with COPD have increased airway eosinophilic inflammation.¹⁵³ The presence of eosinophilic inflammation is best quantified using the direct examination of lung biopsies, bronchoalveolar lavage fluid, and induced sputum, and airway eosinophilia is associated with increased frequency of exacerbations and hospitalizations for exacerbations.^{154,155} Peripheral

blood eosinophilia has been advanced as a more practical surrogate marker for eosinophilic airway inflammation due to the expense and challenge and lack of availability of more directed measurements of airway inflammation. The blood eosinophil count is a promising biomarker of response to inhaled corticosteroids in COPD. The lung has tissue-resident eosinophils that are independent of those recruited by chemokine CCL5. While the origin is different, these two populations share similarities in function.¹⁵⁶ Eosinophils are activated by smoke and infectious byproducts, resulting in the production of the cytokines thymic stromal lymphopoietin (TSLP) and IL-33. TSLP and IL-33 are responsible for recruiting Th2 cells and type 2 innate lymphoid cells (ILC2), which result in eosinophilic inflammation for secreted IL-5.¹⁴⁸ In addition to their effector functions, eosinophils contribute to the immune response through recruitment of dendritic cells (DCs), production of several Th2 chemoattractants, and by performing some functions of antigen presentation.^{156–158}

While knowledge of the role of DCs is not as established, they appear to be important in the pathogenesis of COPD. DCs are antigen-presenting cells that impact the activation of adaptive immune cells. It has been shown that once they are primed, DCs in COPD play a role in increasing natural killer (NK) cell cytotoxicity toward epithelial cells.¹⁵⁹ Lung DCs increasing NK cell activity may be significant in COPD pathogenesis. Like alveolar macrophages, DCs are critical to the balance of inflammatory and anti-inflammatory effects.¹⁶⁰ The overall effect of DCs is critical to both the innate immune response and initiating adaptive immune responses.¹⁶¹

While not all people with chronic tobacco exposure develop COPD, in those who develop COPD, the inflammatory process initiated by smoking may persist long after smoking has stopped.^{147,162,163} The inflammatory processes in COPD are not limited to the lungs and airways. The role of systemic inflammation is evident in stable COPD and to a higher degree in severe COPD and during acute exacerbations of COPD. Systemic inflammation is evident from increased leukocyte counts, cytokines, chemokines, acute phase reactants, or abnormalities in circulating cells.^{163–166}

The various contributions from the immune system cells likely contribute to pathogenesis at separate stages and likely impact the different disease phenotypes. The innate immune response mechanisms contribute to COPD progression, and these mechanisms are interlinked with the activity of adaptive immune cells lead to increased COPD severity.

Acquired Immune Responses

Cellular and humoral immunity are also involved in COPD pathogenesis and the continued progression of COPD after smoking cessation. These COPD responses include the proliferation of B and T cells after antigen presentation by macrophages and dendritic cells. Patients with COPD have an increased presence of cytotoxic CD8+ T cells, various CD4+ subsets including Th1 and Th17, and alterations in T regulatory cells (TREGs).¹⁴⁰ In addition to the role of T cells, antigen exposure elicits B cell responses and antibody production. Further, in the past decade, there has been an increase in information about the function of other adaptive immune cells such as natural killer (NK) cells and natural killer T (NKT) cells in COPD. These inflammatory mediators play a different role and are impacted by smoking status and frequency of respiratory infections and exacerbations, as well as the balance of immunoregulatory cell functions.

CD4+ and CD8+ T cells and B cells accumulate in alveolar and airway tissue in COPD. Peribronchial lymphoid follicles are formed through lymphoid neogenesis and the activity of lymphoid chemokines that are important for cell migration such as CCL21, CXCL12, and CXCL13.^{167,168} There is an accepted role for autoimmunity, particularly in COPD, as evidenced by an excess of

TABLE 38-2 Proteinases That May Affect the Lung Parenchyma

| Proteinase | Cell of Origin |
|------------------------------|---|
| Neutrophil elastase | Neutrophil (monocyte) |
| Proteinase 3 | Neutrophil (monocyte) |
| Cathepsin G | Neutrophil (monocyte, mast cell) |
| MMP-1 ^a | Macrophage, epithelial cell |
| MMP-9 (Gelatinase B) | Macrophage, neutrophil, eosinophil, fibroblast, epithelial cell |
| MMP-12 (Macrophage elastase) | Macrophage |
| Cathepsin L | Macrophage |
| Cathepsin S | Macrophage |

Parentheses denote minor cellular sources.

^aLacks elastase activity.

B cell lymphoid follicles and the presence of several autoantibodies in patients with COPD.^{167,169} Antigens for immunologically mediated progression of airway disease and emphysema include microbial pathogens, peptides altered by tobacco smoke, and peptides released from damaged lung extracellular matrix.^{162,170,171} Difficulties in distinguishing cellular and humoral responses to microbial colonization of advanced airway disease in COPD from pathologic self-directed immune responses will require further study.¹⁶⁷ Due to the complexity and multiplicative nature of the derangements in the immune response in COPD, identifying a therapeutic target, specifically in advanced disease, has been challenging. Targeting therapies in the early stages of disease progression can be a more fruitful endeavor.¹⁷²

■ Proteinase-Antiproteinase Imbalance

The discovery of α -1-AT deficiency-associated early-onset emphysema and the advent of experimental animal models producing emphysema with elastolytic enzymes promoted the imbalance of proteinases relative to their inhibitors as a critical factor for emphysema development.⁹⁴ Proteinases of several biochemical classes, and various specific inhibitors, are implicated in emphysema pathogenesis. Serine proteinases, especially neutrophil elastase and several matrix metalloproteinases, have been the proteinases for which there are the most data¹⁷³ (Table 38-2). It is notable that both neutrophils, which are the source of neutrophil elastase, and MMP-12 from alveolar macrophages are primarily related to continued smoking. Progression after smoking cessation may follow different pathways. Although neutrophil elastase and its main inhibitor α -1-AT have predominated the proteinase–antiproteinase imbalance hypothesis, MMPs appear prominent in mouse models and samples from smokers and individuals with COPD. It is likely a combination of many local imbalances involving several proteinases and antiproteinases contributing to progressive lung destruction.

Several aspects of proteinases in COPD should be noted, as solely a straightforward destructive mechanism is likely an oversimplification. In addition to the destruction of lung elastin and other matrix components, proteinases process cytokines and surface receptors involved in the inflammatory and immune responses.¹⁷⁴ Inflammatory cells may not be the exclusive protein source, as structural cells also produce matrix-degrading proteinases.^{174,175}

■ Oxidant-Antioxidant Imbalance

Reactive oxygen species in cigarette smoke or released by inflammatory cells and the lungs' structural cells in response to smoke may

lead to lung injury.¹⁷⁶ Smoking causes both regional and systemic oxidative stress by altering the balance between oxidants and antioxidants. A puff of cigarette smoke can contain more than 1000 free radicals with more than 4000 oxidant compounds such as superoxides, epoxides, peroxides, nitric oxide (NO; 500 to 1000 ppm), nitrogen dioxide, peroxynitrite (ONOO⁻), and peroxyacetyl nitrates.¹⁷⁷⁻¹⁸⁰ Cigarette smoke-induced oxidative stress initiates a cascade of cellular and molecular reactions that initiate inflammation, cell injury, and apoptosis.¹⁸¹ The processing of these cigarette smoking sequelae is dependent on the effect of antioxidants. Genetic mutations in antioxidant genes are linked to susceptibility and COPD severity. Genetic polymorphisms in antioxidant genes are associated with the progression of COPD, such as polymorphisms in several genes in the glutathione S-transferase (GST) gene family, including GSTM1, GSTM3, GSTP1 as well as superoxide dismutase 3 (SOD3), and microsomal epoxide hydrolase (EPHX1).^{176,182-184} Mutations in transforming growth factor- β 1 (TGFB1) are protective.¹⁸⁵

The lung tissue of smokers contains significantly higher iron content, which provides a catalyst for the production of hydroxyl radicals from H₂O₂.^{186,187} This is combined with the knowledge that iron-responsive element-binding protein 2 (IREB2) polymorphism is prevalent in smokers with COPD^{188,189} (Fig. 38-6). Smokers also demonstrate increased production of neutrophil myeloperoxidase, capable of yielding oxidized halogens such as hypochlorous acid (HOCl).^{189,190} The harmful effects of oxidants are numerous and include modification and inactivation of protease inhibitors (α -1-AT and secretory leukoprotease inhibitor) and anti-inflammatory proteins like histone deacetylase 2 (HDAC2).¹⁹¹⁻¹⁹³ Oxidants can also affect lipids and DNA, and some specific end products, such as 4-hydroxy-2-nonenal (4-HNE) and 8-hydroxy-2'-deoxyguanosine (8-OHdG), may be biomarkers of COPD.^{194,195}

Oxidants can promote inflammation and proteinase expression, facilitate proteinase-mediated extracellular matrix degradation by enhancing matrix molecule susceptibility to proteolytic cleavage, and participate in nonenzymatic degradation of matrix molecules like type I collagen. In experimental animals, the combination of cigarette smoke and elastase leads to more significant emphysema than either insult alone, and antioxidant deficiency results in increased susceptibility.¹⁹⁶⁻¹⁹⁸

■ Apoptosis and Senescence

Cellular senescence and apoptosis occur more frequently in COPD than in healthy people due to replicative and stress-related factors. In vitro, cigarette smoke induces apoptosis of alveolar epithelial cells, endothelial cells, lung fibroblasts, and granulocytes. Bicaudal D1 (BICD1) has been identified as a susceptibility gene in COPD, with a polymorphism linked to emphysema (Fig. 38-6), and encodes for a protein essential in autophagy and critical to the apoptosis pathway.^{199,200}

In addition to apoptosis, cellular senescence is important in COPD pathogenesis. Senescence is a state of stable cell cycle arrest, and usually, due to DNA damage, it makes proliferating cells resistant to growth-promoting stimuli.²⁰¹ Senescence is a driving mechanism resulting in the pathogenesis of emphysema. Senescent cells secrete copious inflammatory proteins propagating inflammatory processes and causing more senescence. Changes related to oxidative stress result in the loss of function of silent information regulator (sirtuin) 1. Sirtuin-1 and sirtuin-6 are antiaging molecules whose deacetylation regulates metabolism, increases genomic stability, and reduces cellular stress.^{201,202} In animal models, several other proteins with anti-aging effects have been identified such as senescence marker protein 30 (SMP30), DNA-dependent protein kinase (DNA-PK), and Ku86.²⁰²⁻²⁰⁴ Senescent cells (alveolar, epithelial, and endothelial cells) are prevalent in the lungs of COPD patients.²⁰⁵⁻²⁰⁷ Impaired immunity, increased cancer risk, and

frequent infections are seen when there is senescence of immune cells (immunosenescence). Early data suggest a potential reversal of these processes, and there are several therapeutic interventions under investigation.^{201,208,209}

Mucus Hypersecretion

Airway mucus is a complex mixture of mucins, inflammatory cells, water, soluble mediators, and negatively charged ions. It is usually a protective barrier that is continuously replenished and cleared in healthy people. The negative charge of mucus glycoproteins results in sequestration of proteases, volatile hydrocarbons, and possibly preservation of the hydration of the ciliated layer, resulting in protection of the underlying lung and likely improved carcinogen clearance. Pathologic or excess mucus production, known as chronic mucus hypersecretion, is one of the most common respiratory symptoms in most chronic lung diseases. Obstruction of small airways and chronic inflammation are fundamental features of many chronic lung diseases such as cystic fibrosis (CF), asthma, and COPD. Exacerbations of these lung diseases are associated with increased mucus production. Sputum production and cough are associated with COPD progression and increased risk of exacerbations, and may have implications on mortality.^{210–213}

Mucus production and regulation is a complex process involving cytokines, chemokines, and several inflammatory mediators as well as toxic agents that induce inflammation and reactive oxygen species (TNF- α , IL-1 β , IL-6, IL-9, IL-17, prostaglandins, neutrophil elastase, human airway trypsin, metalloproteinases, lipopolysaccharides, cigarette smoke, and airway pollutants).^{214–218} In COPD, there is hyperplasia of goblet cells and hypertrophy of glands, with an increase in the ratio of glandular mucus cells to serous cells resulting in pathologic changes to mucus production. Several pathogenic mechanisms are associated with the mucus changes, including altering the mucus proteins (MUCs). Like cystic fibrosis, there is an alteration to favor a predominance of MUC5B over the typical MUC5AC form and an increase in the MUC2 form, which is uncommon in normal lung mucus.^{219,220} Additionally, abnormalities in the cystic fibrosis transmembrane conductance regulator (CFTR) have been shown to alter airway mucociliary transport and contribute to COPD disease pathogenesis.^{221–223} In COPD, other alterations in the mucus layer include greater acidity, less mucin glycosylation, and decreased antimicrobial peptides.²²⁰ Mediators responsible for mucus hypersecretion include proteinases, cytokines, oxidants, and activation of several signaling pathways such as epidermal growth factor receptor (EGFR).^{224–227} The small airway luminal obstruction by mucus is correlated with the degree of airflow obstruction and inversely correlated with survival after lung volume reduction surgery.²²⁸

Lung Elastic Fiber Degradation

Observations linking proteinases to emphysema led to the concept that the destruction of alveolar elastic fibers is key to emphysema development.²²⁹ An imbalance of proteases and antiproteinases result in parenchymal destruction. Macrophages, neutrophils, and other effector cells release proteinases, including proteinase 3, matrix metalloproteinases (MMPs), and other cytolytic products that activate each other and inhibit other endogenous inhibitors.²³⁰ Structurally, the extracellular matrix of the lung is organized into three interdependent cable systems: (1) an axial system that extends from the central airways through the peripheral airways to the alveolar ducts; (2) a parenchymal system that comprises the matrix of the alveolar septae; and (3) a peripheral system that arises from the visceral pleura and extends into the interlobular septae, forming a fibrous sac around the lung. Distal to the respiratory bronchioles, the axial system forms a helix encircling the alveolar ducts, extending into the interstitium of alveolar walls. Elastic fibers, of which elastin

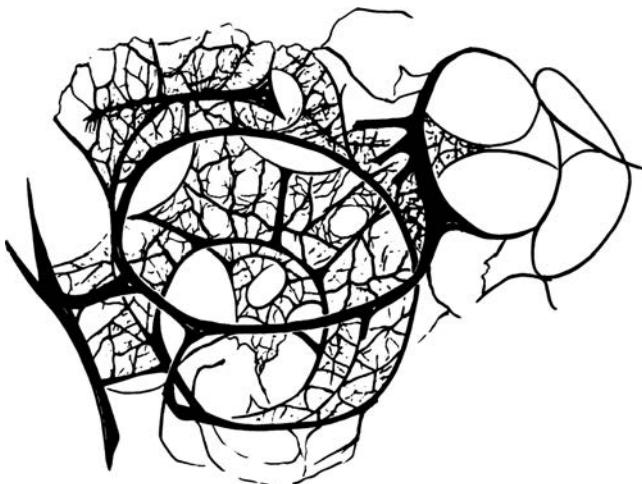


Figure 38-10 Alveolar elastic fiber network. Artist's sketch of the elastic fibers in lung parenchyma showing how elastic fibers form a helix encircling the alveolar ducts and penetrate alveolar septae. (Reproduced with permission from Pierce JA, Ebert RV. Fibrous network of the lung and its change with age. Thorax. 1965;20(5):469–476.)

is the main component, loop around alveolar ducts, form rings at the mouths of the alveoli, and penetrate as wisps into the alveolar septae, where they are concentrated at bends and junctions (Fig. 38-10). Elastic fibers, which possess rubberlike reversible extensibility, come under tension and provide elastic recoil throughout the respiratory cycle. Unlike elastic fibers, the interstitial collagen fibers in alveolar septa are not distensible and have high tensile strength.

Elastin is present in bronchi and lung parenchyma, and in alveolar regions of the lung, elastin fibers are deployed around alveolar ducts, the openings of alveoli, and extensions into alveolar septa.²³¹ Distraction of elastic fibers leads to tissue loss, altered alveolar structure, and emphysema. While elastin is resistant to many proteinases, some enzymes can degrade elastin (Table 38-2). Elastic fibers in the lung typically last an entire human life span.²³² Histologic studies of emphysematous lung tissue support the hypothesis that elastic fibers are perturbed in emphysema. There are fragmented elastic fibers in α 1-AT deficiency and poorly formed elastic fibers, and elastin clumps in smokers with centriacinar emphysema.²³² The latter changes appear from the aberrant synthesis of new elastin and resemble the findings in emphysematous lungs induced experimentally with elastase.

Animal models employing elastase-induced emphysema have shown acute depletion of elastin following an intratracheal injection of human neutrophil elastase, followed by a burst of synthesis of extracellular matrix including elastin.²³³ Over a few weeks, the elastin content of the lungs returns to normal, although the lungs still display emphysema. The elastic fibers, like the elastic fibers in human emphysema, appear disorganized. New elastin gene expression occurs even in severe emphysema in humans (Fig. 38-11). However, there are significant barriers to the effective repair of damaged elastic fibers in the mature lung. When elastic fibers are damaged enough to fail under load, there is no mechanism for cells to recreate a structure with a length many times the size of each cell. The injured adult lung lacks the mechanical and morphogen gradients that initiate alveolar formation during development and may also be unable to coordinate the expression of the many components necessary for functional elastic fiber synthesis.

Lung Collagen Turnover

Although elastic fiber destruction dominates the proteolytic basis for emphysema pathogenesis, the degradation of alveolar wall collagen and aberrant collagen deposition in alveolar tissue also may

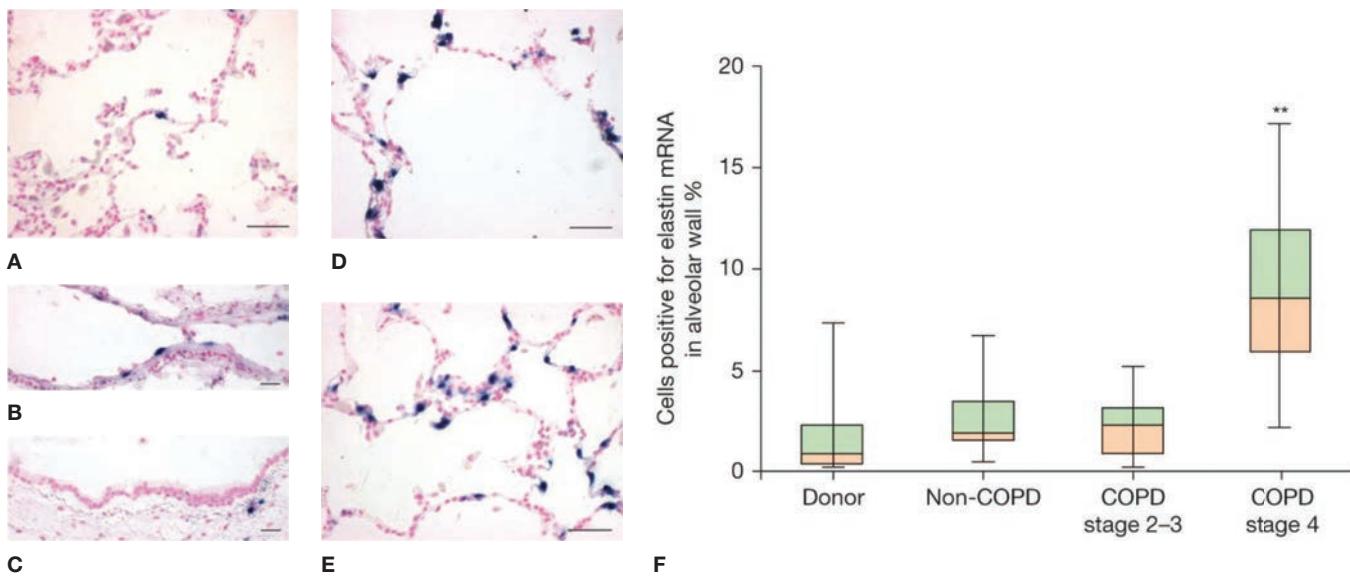


Figure 38-11 Expression of elastin production in severely emphysematous lung removed for lung transplantation. Elastin mRNA (blue signal) as detected by *in situ* hybridization is rarely detected in donor lungs in (A) parenchyma, (B) intralobal pulmonary arteries, or (C) airways but is prevalent in the parenchyma of patients with very severe COPD in regions with moderate (D) and severe (E) alveolar enlarge-

ment. Quantification of cells positive for elastin mRNA (F) reveals significantly higher elastin expression in alveolar walls of very severe COPD (GOLD stage 4) lungs compared with donor lungs or less severe COPD lungs. (Reproduced with permission Deslee G, Woods JC, Moore CM, et al. Elastin expression in very severe human COPD. *Eur Respir J.* 2009;34(2):324–331.)

be involved. There is increased collagen deposition in patients with COPD compared with smoker controls.²³⁴ In some forms of experimental emphysema, collagen destruction appears to be a critical event. Human collagenase/matrix metalloproteinase 1 (MMP-1) is important in development of emphysema. Mice genetically engineered to harbor a transgene that leads to the expression of MMP-1 in lung tissue develop structural changes typical of emphysema. These changes occur due to the destruction of alveolar type III collagen.^{235,236} In these models, emphysema occurs without obvious disruption and faulty resynthesis of elastic fibers as the elastic fibers in these lungs look normal. Expression of MMP-1 by alveolar epithelial cells in human emphysematous tissue fits with the idea that collagenolytic activity plays a role in emphysema.^{175,237}

Cigarette smoke exposure leads to tripeptide proline-glycine-proline (PGP) release from the lung matrix.²³⁸ PGP binds chemokine receptor 2 (CXCR2), a prominent chemokine receptor on neutrophils. PGP functions as a neutrophil chemoattractant, and in an animal model, PGP's repeated instillation into the lung produces emphysema by collagen breakdown.^{238,239} Analogous to elastin peptides promoting emphysema in mice, PGP is generated by the sequential breakdown of collagen by MMPs 8 and 9 and prolyl endopeptidase, and blocking PGP reduces emphysema in mice exposed to cigarette smoke.^{239,240}

In emphysematous lungs, the pores of Kohn are larger and more numerous than in normal lungs (Fig. 38-12). Because interstitial collagens and basement membrane collagens are prominent in alveolar walls, it is plausible that collagenous structures undergo degradation in the process of generating these interalveolar pores.

CONCLUSION

Despite advances in pathogenesis, the treatment options remain limited, with very few options that significantly impact mortality. Unlike many major causes of death, the disease burden is projected to continue to increase as cigarette smoke exposure continues to increase in low- and middle-income countries. Despite the current efforts at decreasing the burden of the disease, there remains a significant need.

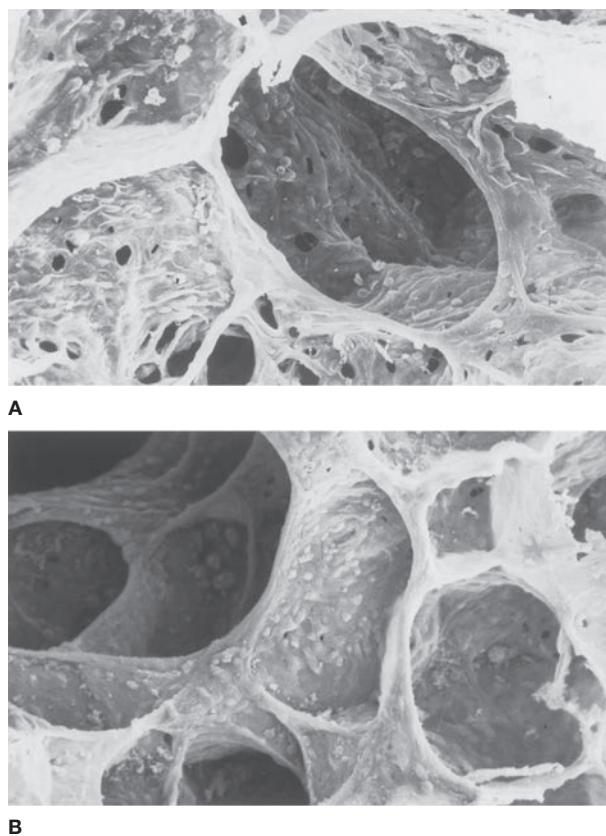


Figure 38-12 Holes in alveolar walls in early emphysema. Scanning electron micrographs of alveolar walls from surgically resected specimens: lung with mild emphysema (A) and nonemphysematous lung (B). Holes are more numerous in alveolar walls in the emphysematous lung than in the normal lung. Original magnification $\times 250$. (Reproduced with permission from Nagai A, Inano H, Matsuba K, et al. Scanning electron microscopic morphometry of emphysema in humans. *Am J Respir Crit Care Med.* 1994;150(5 Pt 1):1411–1415.)

REFERENCES

- Singh D, Agusti A, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J.* 2019;53(5):1900164.
- Morgagni G. The seats and causes of diseases investigated by anatomy; in five books, containing a great variety of dissections, with remarks. To which are added very accurate and copious indexes of the principal things and names therein contained. Vol. 2. London: Printed for A. Millar, and T. Cadell, his successor [etc.]; 1769.
- Güder G, Brenner S, Angermann CE, et al. GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res.* 2012;13(1):13.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319–338.
- Çolak Y, Nordestgaard BG, Vestbo J, et al. Comparison of five major airflow limitation criteria to identify high-risk individuals with COPD: a contemporary population-based cohort. *Thorax.* 2020;75(11):944–954.
- Bhatt SP, Balte PP, Schwartz JE, et al. Discriminative accuracy of FEV1: FVC thresholds for COPD-related hospitalization and mortality. *JAMA.* 2019;321(24):2438–2447.
- Lowe KE, Regan EA, Anzueto A, et al. COPDGene® 2019: redefining the diagnosis of chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis.* 2019;6(5):384.
- Woodruff PG, Barr RG, Bleeker E, et al. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med.* 2016;374(19):1811–1821.
- Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004;23(6):932–946.
- Soriano JB, Kendrick PJ, Paulson KR, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med.* 2020;8(6):585–596.
- Bloom DE, Cafiero E, Jané-Llopis E, et al. *The Global Economic Burden of Noncommunicable Diseases.* Geneva: World Economic Forum; 2011.
- 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.* London: Oxford University Press; 1976.
- Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(45):1013.
- Centers for Disease Control and Prevention. Current cigarette smoking among adults in the United States. www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/. Accessed January 7, 2022.
- Jha P, MacLennan M, Chaloupka FJ, et al. Global Hazards of Tobacco and the Benefits of Smoking Cessation and Tobacco Taxes. In: Gelband H, Jha P, Sankaranarayanan R, Horton S, eds. *Cancer: Disease Control Priorities.* Washington, DC: International Bank for Reconstruction and Development /The World Bank; 2015.
- Salvi S, Barnes PJ. Is exposure to biomass smoke the biggest risk factor for COPD globally? *Chest.* 2010;138(1):3–6.
- Eisner MD, Anthonisen N, Coulas D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2010;182(5):693–718.
- Brandsma C-A, de Vries M, Costa R, et al. Lung ageing and COPD: is there a role for ageing in abnormal tissue repair? *Eur Respir Rev.* 2017;26(146).
- Kurmi OP, Semple S, Simkhada P, et al. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. *Thorax.* 2010;65(3):221–228.
- Andersen ZJ, Hvidberg M, Jensen SS, et al. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. *Am J Respir Crit Care Med.* 2011;183(4):455–461.
- Fullerton DG, Bruce N, Gordon SB. Indoor air pollution from biomass fuel smoke is a major health concern in the developing world. *Trans R Soc Trop Med Hyg.* 2008;102(9):843–851.
- Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet.* 2009;374(9691):733–743.
- Sood A, Assad NA, Barnes PJ, et al. ERS/ATS workshop report on respiratory health effects of household air pollution. *Eur Respir J.* 2018;51(1).
- Diab N, Gershon AS, Sin DD, et al. Underdiagnosis and overdiagnosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2018;198(9):1130–1139.
- Ejike CO, Dransfield MT, Hansel NN, et al. Chronic obstructive pulmonary disease in America's black population. *Am J Respir Crit Care Med.* 2019;200(4):423–430.
- Wheaton AG, Liu Y, Croft JB, et al. Chronic obstructive pulmonary disease and smoking status—United States, 2017. *MMWR Morb Mortal Wkly Rep.* 2019;68(24):533.
- Centers for Disease Control and Prevention. The Behavioral Risk Factor Surveillance System 2017 summary data quality report. Atlanta, GA: Centers for Disease Control and Prevention; 2018.
- Martinez CH, Mannino DM, Jaimes FA, et al. Undiagnosed obstructive lung disease in the United States. Associated factors and long-term mortality. *Ann Am Thorac Soc.* 2015;12(12):1788–1795.
- Mintz ML, Yawn BP, Mannino DM, et al. Prevalence of airway obstruction assessed by lung function questionnaire. *Mayo Clin Proc.* 2011;86(5):375–381.
- Shavelle RM, Paculdo DR, Kush SJ, et al. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. *Int J Chron Obstruct Pulmon Dis.* 2009;4:137.
- Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med.* 2019;7(4):358–364.
- Celli BR, Agustí A. COPD: time to improve its taxonomy? *ERJ Open Res.* 2018;4(1).
- Lamprecht B, McBurnie MA, Vollmer WM, et al. COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest.* 2011;139(4):752–763.
- Hooper R, Burney P, Vollmer WM, et al. Risk factors for COPD spirometrically defined from the lower limit of normal in the BOLD project. *Eur Respir J.* 2012;39(6):1343–1353.
- Blanc PD, Eisner MD, Earnest G, et al. Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. *J Occup Environ Med.* 2009;51(7):804.
- de Marco R, Accordini S, Antò JM, et al. Long-term outcomes in mild/moderate chronic obstructive pulmonary disease in

- the European community respiratory health survey. *Am J Respir Crit Care Med.* 2009;180(10):956–963.
37. Mathew AR, Bhatt SP, Colangelo LA, et al. Life-course smoking trajectories and risk for emphysema in middle age: the CARDIA Lung study. *Am J Respir Crit Care Med.* 2019;199(2):237–240.
38. Etter J-F, Perneger T. Measurement of self reported active exposure to cigarette smoke. *J Epidemiol Community Health.* 2001;55(9):674–680.
39. Gold DR, Wang X, Wypij D, et al. Effects of cigarette smoking on lung function in adolescent boys and girls. *N Engl J Med.* 1996;335(13):931–937.
40. Pirie K, Peto R, Reeves GK, et al. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet.* 2013;381(9861):133–141.
41. Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med.* 2015;373(2):111–122.
42. DeMeo DL, Ramagopalan S, Kavati A, et al. Women manifest more severe COPD symptoms across the life course. *Int J Chron Obstruct Pulmon Dis.* 2018;13:3021.
43. Prescott E, Bjerg AM, Andersen PK, et al. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J.* 1997;10(4):822–827.
44. Foreman MG, Zhang L, Murphy J, et al. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. *Am J Respir Crit Care Med.* 2011;184(4):414–420.
45. Chatila WM, Wynkoop WA, Vance G, Criner GJ. Smoking patterns in African Americans and whites with advanced COPD. *Chest.* 2004;125(1):15–21.
46. Drummond MB, Hansel NN, Connell JE, et al. Spirometric predictors of lung function decline and mortality in early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012;185(12):1301–1306.
47. Casanova C, de Torres JP, Aguirre-Jaime A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. *Am J Respir Crit Care Med.* 2011;184(9):1015–1021.
48. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med.* 2011;365(13):1184–1192.
49. Sheng L, Tu J-W, Tian J-H, et al. A meta-analysis of the relationship between environmental tobacco smoke and lung cancer risk of nonsmoker in China. *Medicine (Baltimore).* 2018;97(28):e11389.
50. Tsai J, Homa DM, Gentzke AS, et al. Exposure to secondhand smoke among nonsmokers—United States, 1988–2014. *MMWR Morb Mortal Wkly Rep.* 2018;67(48):1342.
51. Law MR, Morris J, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *BMJ.* 1997;315(7114):973–980.
52. Azagba S, Latham K, Shan L. Sociodemographic differences in secondhand smoke exposure in the United States. *Health Educ Behav.* 2020;47(4):602–610.
53. DiFranza JR, Aligne CA, Weitzman M. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics.* 2004;113(4 Suppl):1007–1015.
54. Johannessen A, Bakke PS, Hardie JA, Eagan TM. Association of exposure to environmental tobacco smoke in childhood with chronic obstructive pulmonary disease and respiratory symptoms in adults. *Respirology.* 2012;17(3):499–505.
55. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. *Lancet.* 2015;385(9971):899–909.
56. Jamieson DB, Matsui EC, Belli A, et al. Effects of allergic phenotype on respiratory symptoms and exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2013;188(2):187–192.
57. Guo C, Zhang Z, Lau AK, et al. Effect of long-term exposure to fine particulate matter on lung function decline and risk of chronic obstructive pulmonary disease in Taiwan: a longitudinal cohort study. *Lancet Planet Health.* 2018;2(3):e114–e125.
58. Smith-Sivertsen T, Diaz E, Pope D, et al. Effect of reducing indoor air pollution on women's respiratory symptoms and lung function: the RESPIRE Randomized Trial, Guatemala. *Am J Epidemiol.* 2009;170(2):211–220.
59. Mannucci PM, Franchini M. Health effects of ambient air pollution in developing countries. *Int J Environ Res Public Health.* 2017;14(9):1048.
60. World Health Organization. Household air pollution and health. Geneva: World Health Organization; 2021.
61. Lytras T, Kogevinas M, Kromhout H, et al. Occupational exposures and 20-year incidence of COPD: the European Community Respiratory Health Survey. *Thorax.* 2018;73(11):1008–1015.
62. Naidoo RN. Occupational exposures and chronic obstructive pulmonary disease: incontrovertible evidence for causality? *Am J Respir Crit Care Med.* 2012;185(12):1252–1254.
63. Mehta AJ, Miedinger D, Keidel D, et al. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. *Am J Respir Crit Care Med.* 2012;185(12):1292–1300.
64. Sadhra S, Kurmi OP, Sadhra SS, et al. Occupational COPD and job exposure matrices: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis.* 2017;12:725–734.
65. Patel CJ, Kerr J, Thomas DC, et al. Opportunities and challenges for environmental exposure assessment in population-based studies. *Cancer Epidemiol Biomarkers Prev.* 2017;26(9):1370–1380.
66. Bello A, Quinn MM, Perry MJ, Milton DK. Quantitative assessment of airborne exposures generated during common cleaning tasks: a pilot study. *Environ Health.* 2010;9:76.
67. Siemiatycki J, Lavoué J. Availability of a new job-exposure matrix (CANJEM) for epidemiologic and occupational medicine purposes. *J Occup Environ Med.* 2018;60(7):e324–e328.
68. Benke G, Sim M, Fritschi L, Aldred G. Beyond the job exposure matrix (JEM): the task exposure matrix (TEM). *Ann Occup Hyg.* 2000;44(6):475–482.
69. Mehta AJ, Miedinger D, Keidel D, et al. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. *Am J Respir Crit Care Med.* 2012;185(12):1292–1300.
70. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol.* 2002;156(8):738–746.
71. Sharp RR, de Serres F, Newman L, et al. Environmental, occupational, and genetic risk factors for alpha-1 antitrypsin deficiency. *Environ Health Perspect.* 2003;111(14):1749–1752.

72. Robertson NM, Nagourney EM, Pollard SL, et al. Urban-rural disparities in chronic obstructive pulmonary disease management and access in Uganda. *Chronic Obstr Pulm Dis.* 2019;6(1):17–28.
73. Raju S, Keet CA, Paulin LM, et al. Rural residence and poverty are independent risk factors for chronic obstructive pulmonary disease in the United States. *Am J Respir Crit Care Med.* 2019;199(8):961–969.
74. Mehrotra A, Akanbi MO, Gordon SB. The burden of COPD in Africa: a literature review and prospective survey of the availability of spirometry for COPD diagnosis in Africa. *Trop Med Int Health.* 2009;14(8):840–848.
75. Galiatsatos P, Woo H, Paulin LM, et al. The association between neighborhood socioeconomic disadvantage and chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2020;15:981–993.
76. Jamal A, King BA, Neff LJ, et al. Current cigarette smoking among adults—United States, 2005–2015. *MMWR Morb Mortal Wkly Rep.* 2016;65(44):1205–1211.
77. World Health Organization. *Global Tuberculosis Report 2019.* Geneva: World Health Organization; 2019.
78. Jin J, Li S, Yu W, et al. Emphysema and bronchiectasis in COPD patients with previous pulmonary tuberculosis: computed tomography features and clinical implications. *Int J Chron Obstruct Pulmon Dis.* 2018;13:375–384.
79. Yakar HI, Gunen H, Pehlivan E, Aydogan S. The role of tuberculosis in COPD. *Int J Chron Obstruct Pulmon Dis.* 2017;12:323–329.
80. Kuhlman JE, Knowles MC, Fishman EK, Siegelman SS. Premature bullous pulmonary damage in AIDS: CT diagnosis. *Radiology.* 1989;173(1):23–26.
81. Fitzpatrick ME, Kunisaki KM, Morris A. Pulmonary disease in HIV-infected adults in the era of antiretroviral therapy. *AIDS.* 2018;32(3):277–292.
82. Gingo MR, He J, Wittman C, et al. Contributors to diffusion impairment in HIV-infected persons. *Eur Respir J.* 2014;43(1):195–203.
83. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med.* 2011;183(3):388–395.
84. Ronit A, Kristensen T, Hoseth VS, et al. Computed tomography quantification of emphysema in people living with HIV and uninfected controls. *Eur Respir J.* 2018;52(1):1800296.
85. Aukrust P, Muller F, Svartdal AM, et al. Disturbed glutathione metabolism and decreased antioxidant levels in human immunodeficiency virus-infected patients during highly active antiretroviral therapy—potential immunomodulatory effects of antioxidants. *J Infect Dis.* 2003;188(2):232–238.
86. Desai S, Landay A. Early immune senescence in HIV disease. *Curr HIV/AIDS Rep.* 2010;7(1):4–10.
87. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med.* 2011;62:141–155.
88. Almodovar S, Hsue PY, Morelli J, et al. Pathogenesis of HIV-associated pulmonary hypertension: potential role of HIV-1 Nef. *Proc Am Thorac Soc.* 2011;8(3):308–312.
89. Morris A, Gingo MR, George MP, et al. Cardiopulmonary function in individuals with HIV infection in the antiretroviral therapy era. *AIDS.* 2012;26(6):731–740.
90. Stern DA, Morgan WJ, Wright AL, et al. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet.* 2007;370(9589):758–764.
91. Wilk JB, Djousse L, Arnett DK, et al. Evidence for major genes influencing pulmonary function in the NHLBI family heart study. *Genet Epidemiol.* 2000;19(1):81–94.
92. Palmer LJ, Knuiman MW, Divitini ML, et al. Familial aggregation and heritability of adult lung function: results from the Busselton Health Study. *Eur Respir J.* 2001;17(4):696–702.
93. Zhou JJ, Cho MH, Castaldi PJ, et al. Heritability of chronic obstructive pulmonary disease and related phenotypes in smokers. *Am J Respir Crit Care Med.* 2013;188(8):941–947.
94. Laurell C-B, Eriksson S. The electrophoretic $\alpha 1$ -globulin pattern of serum in $\alpha 1$ -antitrypsin deficiency. *Scand J Clin Lab Invest.* 1963;15(2):132–140.
95. Silverman EK, Sandhaus RA. Alpha1-antitrypsin deficiency. *N Engl J Med.* 2009;360(26):2749–2757.
96. Green C, Vayalapra S, Hampson J, et al. PiSZ alpha-1 antitrypsin deficiency (AATD): pulmonary phenotype and prognosis relative to PiZZ AATD and PiMM COPD. *Thorax.* 2015;70(10):939–945.
97. Turino GM, Barker AF, Brantly ML, et al. Clinical features of individuals with PI*SZ phenotype of alpha 1-antitrypsin deficiency. *alpha 1-Antitrypsin Deficiency Registry Study Group. Am J Respir Crit Care Med.* 1996;154(6 Pt 1):1718–1725.
98. Ortega VE, Li X, O'Neal WK, et al. The effects of rare SERPINA1 variants on lung function and emphysema in SPIROMICS. *Am J Respir Crit Care Med.* 2020;201(5):540–554.
99. Sørheim I-C, Bakke P, Gulsvik A, et al. α ; 1-Antitrypsin protease inhibitor MZ heterozygosity is associated with airflow obstruction in two large cohorts. *Chest.* 2010;138(5):1125–1132.
100. Castaldi PJ, Demeo DL, Hersh CP, et al. Impact of non-linear smoking effects on the identification of gene-by-smoking interactions in COPD genetics studies. *Thorax.* 2011;66(10):903–909.
101. DeMeo DL, Campbell EJ, Brantly ML, et al. Heritability of lung function in severe alpha-1 antitrypsin deficiency. *Hum Hered.* 2009;67(1):38–45.
102. Armanios M, Chen JL, Chang YP, et al. Haplodeficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita. *Proc Natl Acad Sci U S A.* 2005;102(44):15960–15964.
103. Stanley SE, Chen JJ, Podlevsky JD, et al. Telomerase mutations in smokers with severe emphysema. *J Clin Invest.* 2015;125(2):563–570.
104. Stanley SE, Merck SJ, Armanios M. Telomerase and the genetics of emphysema susceptibility. Implications for pathogenesis paradigms and patient care. *Ann Am Thorac Soc.* 2016;13(Suppl 5):S447–S451.
105. Stanley SE, Chen JJ, Podlevsky JD, et al. Telomerase mutations in smokers with severe emphysema. *J Clin Invest.* 2015;125(2):563–570.
106. Nunes H, Monnet I, Kannengiesser C, et al. Is telomeropathy the explanation for combined pulmonary fibrosis and emphysema syndrome?: report of a family with TERT mutation. *Am J Respir Crit Care Med.* 2014;189(6):753–754.
107. Li Y, Cho MH, Zhou X. What do polymorphisms tell us about the mechanisms of COPD? *Clin Sci.* 2017;131(24):2847–2863.
108. Wilk JB, Walter RE, Laramie JM, et al. Framingham Heart Study genome-wide association: results for pulmonary function measures. *BMC Med Genet.* 2007;8(S1):S8.
109. Brantly M, Nukiwa T, Crystal RG. Molecular basis of alpha-1-antitrypsin deficiency. *Am J Med.* 1988;84(6A):13–31.

110. Yim JJ, Park GY, Lee CT, et al. Genetic susceptibility to chronic obstructive pulmonary disease in Koreans: combined analysis of polymorphic genotypes for microsomal epoxide hydrolase and glutathione S-transferase M1 and T1. *Thorax*. 2000;55(2):121–125.
111. Siedlinski M, Cho MH, Bakke P, et al. Genome-wide association study of smoking behaviours in patients with COPD. *Thorax*. 2011;66(10):894–902.
112. Cho MH, Castaldi PJ, Wan ES, et al. A genome-wide association study of COPD identifies a susceptibility locus on chromosome 19q13. *Hum Mol Genet*. 2012;21(4):947–957.
113. Hancock DB, Eijgelsheim M, Wilk JB, et al. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. *Nat Genet*. 2010;42(1):45–52.
114. Moll M, Sakornsakolpat P, Shrine N, et al. Chronic obstructive pulmonary disease and related phenotypes: polygenic risk scores in population-based and case-control cohorts. *Lancet Respir Med*. 2020;8(7):696–708.
115. Oelsner EC, Ortega VE, Smith BM, et al. A genetic risk score associated with chronic obstructive pulmonary disease susceptibility and lung structure on computed tomography. *Am J Respir Crit Care Med*. 2019;200(6):721–731.
116. Silverman EK. Genetics of COPD. *Annu Rev Physiol*. 2020;82(1):413–431.
117. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med*. 1968;278(25):1355–1360.
118. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645–2653.
119. McDonough JE, Yuan R, Suzuki M, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med*. 2011;365(17):1567–1575.
120. Bhatt SP, Soler X, Wang X, et al. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2016;194(2):178–184.
121. Galbán CJ, Han MK, Boes JL, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med*. 2012;18(11):1711.
122. Berger KI, Pradhan DR, Goldring RM, et al. Distal airway dysfunction identifies pulmonary inflammation in asymptomatic smokers. *ERJ Open Res*. 2016;2(4):00066–02016.
123. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet*. 2004;364(9435):709–721.
124. Make BJ. COPD: a new diagnostic paradigm. *Chronic Obstr Pulm Dis*. 2019;6(5):438.
125. Fortis S, Comellas A, Kim V, et al. Low FVC/TLC in preserved ratio impaired spirometry (PRISm) is associated with features of and progression to obstructive lung disease. *Sci Rep*. 2020;10(1):1–11.
126. Kessler R, Partridge MR, Miravitles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J*. 2011;37(2):264–272.
127. Scichilone N, Battaglia S, La Sala A, Bellia V. Clinical implications of airway hyper-responsiveness in COPD. *Int J Chron Obstruct Pulmon Dis*. 2006;1(1):49.
128. Bellofiore S, Eidelman DH, Macklem PT, Martin JG. Effects of elastase-induced emphysema on airway responsiveness to methacholine in rats. *J Appl Physiol*. 1989;66(2):606–612.
129. Tashkin DP, Altose MD, Connell JE, et al. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med*. 1996;153(6 Pt 1):1802–1811.
130. Anthonisen NR, Lindgren PG, Tashkin DP, et al. Bronchodilator response in the lung health study over 11 yrs. *Eur Respir J*. 2005;26(1):45–51.
131. Higham A, Quinn AM, Cançado JED, Singh D. The pathology of small airways disease in COPD: historical aspects and future directions. *Respir Res*. 2019;20(1):1–11.
132. Kuwano K, Bosken CH, Pare PD, et al. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1993;148(5):1220–1225.
133. Sethi S, Maloney J, Grove L, et al. Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2006;173(9):991–998.
134. Röpcke S, Holz O, Lauer G, et al. Repeatability of and relationship between potential COPD biomarkers in bronchoalveolar lavage, bronchial biopsies, serum, and induced sputum. *PLoS One*. 2012;7(10):e46207.
135. Fens N, de Nijs SB, Peters S, et al. Exhaled air molecular profiling in relation to inflammatory subtype and activity in COPD. *Eur Respir J*. 2011;38(6):1301–1309.
136. Di Stefano A, Capelli A, Lusuardi M, et al. Severity of airflow limitation is associated with severity of airway inflammation in smokers. *Am J Respir Crit Care Med*. 1998;158(4):1277–1285.
137. O'Shaughnessy TC, Ansari TW, Barnes NC, Jeffery PK. Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T lymphocytes with FEV1. *Am J Respir Crit Care Med*. 1997;155(3):852–857.
138. Kirkham PA, Barnes PJ. Oxidative stress in COPD. *Chest*. 2013;144(1):266–273.
139. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. *Clin Sci*. 2017;131(13):1541–1558.
140. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol*. 2008;8(3):183–192.
141. Traves SL, Smith SJ, Barnes PJ, Donnelly LE. Specific CXC but not CC chemokines cause elevated monocyte migration in COPD: a role for CXCR2. *J Leukoc Biol*. 2004;76(2):441–450.
142. Barnawi J, Tran H, Jersmann H, et al. Potential link between the sphingosine-1-phosphate (S1P) system and defective alveolar macrophage phagocytic function in chronic obstructive pulmonary disease (COPD). *PLoS One*. 2015;10(10):e0122771.
143. Eapen MS, Hansbro PM, McAlinden K, et al. Abnormal M1/M2 macrophage phenotype profiles in the small airway wall and lumen in smokers and chronic obstructive pulmonary disease (COPD). *Sci Rep*. 2017;7(1):1–12.
144. Lea SR, Reynolds SL, Kaur M, et al. The effects of repeated Toll-like receptors 2 and 4 stimulation in COPD alveolar macrophages. *Int J Chron Obstruct Pulmon Dis*. 2018;13:771.
145. Finlay GA, O'Driscoll LR, Russell KJ, et al. Matrix metalloproteinase expression and production by alveolar macrophages in emphysema. *Am J Respir Crit Care Med*. 1997;156(1):240–247.
146. Asthana A, Johnson HM, Piper ME, et al. Effects of smoking intensity and cessation on inflammatory markers in a large cohort of active smokers. *Am Heart J*. 2010;160(3):458–463.

147. Marques LJ, Teschler H, Guzman J, Costabel U. Smoker's lung transplanted to a nonsmoker. Long-term detection of smoker's macrophages. *Am J Respir Crit Care Med.* 1997;156(5):1700–1702.
148. Barnes PJ. Inflammatory endotypes in COPD. *Allergy.* 2019;74(7):1249–1256.
149. Quint JK, Wedzicha JA. The neutrophil in chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2007;119(5):1065–1071.
150. Culpitt SV, Maziak W, Loukidis S, et al. Effect of high dose inhaled steroid on cells, cytokines, and proteases in induced sputum in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1999;160(5):1635–1639.
151. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2016;138(1):16–27.
152. Gross NJ, Barnes PJ. New therapies for asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2017;195(2):159–166.
153. Saha S, Brightling CE. Eosinophilic airway inflammation in COPD. *Int J Chron Obstruct Pulmon Dis.* 2006;1(1):39–47.
154. Couillard S, Larivee P, Courteau J, Vanasse A. Eosinophils in COPD exacerbations are associated with increased readmissions. *Chest.* 2017;151(2):366–373.
155. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med.* 2012;186(1):48–55.
156. Weller PF, Spencer LA. Functions of tissue-resident eosinophils. *Nat Rev Immunol.* 2017;17(12):746–760.
157. Dajotoy T, Andersson P, Bjartell A, et al. Human eosinophils produce the T cell-attracting chemokines MIG and IP-10 upon stimulation with IFN- γ . *J Leukoc Biol.* 2004;76(3):685–691.
158. Farhan RK, Vickers MA, Ghaemmaghami AM, et al. Effective antigen presentation to helper T cells by human eosinophils. *Immunology.* 2016;149(4):413–422.
159. Finch DK, Stolberg VR, Ferguson J, et al. Lung dendritic cells drive natural killer cytotoxicity in chronic obstructive pulmonary disease via IL-15Ra. *Am J Respir Crit Care Med.* 2018;198(9):1140–1150.
160. Givi ME, Redegeld FA, Folkerts G, Mortaz E. Dendritic cells in pathogenesis of COPD. *Curr Pharm Des.* 2012;18(16):2329–2335.
161. Freeman CM, Curtis JL. Lung dendritic cells: shaping immune responses throughout chronic obstructive pulmonary disease progression. *Am J Respir Cell Mol Biol.* 2017;56(2):152–159.
162. Lee S-H, Goswami S, Grudo A, et al. Antielastin autoimmunity in tobacco smoking-induced emphysema. *Nat Med.* 2007;13(5):567–569.
163. Gan WQ, Man S, Senthilselvan A, Sin D. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax.* 2004;59(7):574–580.
164. Cockayne DA, Cheng DT, Waschki B, et al. Systemic biomarkers of neutrophilic inflammation, tissue injury and repair in COPD patients with differing levels of disease severity. *PLoS One.* 2012;7(6):e38629.
165. Fontes JD, Yamamoto JF, Larson MG, et al. Clinical correlates of change in inflammatory biomarkers: The Framingham Heart Study. *Atherosclerosis.* 2013;228(1):217–223.
166. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J.* 2009;33(5):1165–1185.
167. Brusselle G, Demoer T, Bracke K, et al. Lymphoid follicles in (very) severe COPD: beneficial or harmful? *Eur Respir J.* 2009;34(1):219–230.
168. Luther SA, Bidgol A, Hargreaves DC, et al. Differing activities of homeostatic chemokines CCL19, CCL21, and CXCL12 in lymphocyte and dendritic cell recruitment and lymphoid neogenesis. *J Immunol.* 2002;169(1):424–433.
169. Polverino F, Cosio BG, Pons J, et al. B cell-activating factor. An orchestrator of lymphoid follicles in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2015;192(6):695–705.
170. Houghton AM, Quintero PA, Perkins DL, et al. Elastin fragments drive disease progression in a murine model of emphysema. *J Clin Invest.* 2006;116(3):753–759.
171. Grumelli S, Corry DB, Song LZ, et al. An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema. *PLoS Med.* 2004;1(1):e8.
172. Vogelmeier CF, Román-Rodríguez M, Singh D, et al. Goals of COPD treatment: focus on symptoms and exacerbations. *Respir Med.* 2020;166:105938.
173. Hautamaki RD, Kobayashi DK, Senior RM, Shapiro SD. Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice. *Science.* 1997;277(5334):2002–2004.
174. Barnes PJ, Shapiro SD, Pauwels R. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur Respir J.* 2003;22(4):672–688.
175. Imai K, Dalal SS, Chen ES, et al. Human collagenase (matrix metalloproteinase-1) expression in the lungs of patients with emphysema. *Am J Respir Crit Care Med.* 2001;163(3 Pt 1):786–791.
176. Fischer BM, Voynow JA, Ghio AJ. COPD: balancing oxidants and antioxidants. *Int J Chron Obstruct Pulmon Dis.* 2015;10:261.
177. Pryor WA. Cigarette smoke and the involvement of free radical reactions in chemical carcinogenesis. *Br J Cancer Suppl.* 1987;8:19–23.
178. Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. *Environ Health Perspect.* 1985;64:111–126.
179. Pryor WA. Cigarette smoke radicals and the role of free radicals in chemical carcinogenicity. *Environ Health Perspect.* 1997;105(Suppl 4):875–882.
180. Carnevale R, Sciarretta S, Violi F, et al. Acute impact of tobacco vs electronic cigarette smoking on oxidative stress and vascular function. *Chest.* 2016;150(3):606–612.
181. Rahman I. Oxidative stress in pathogenesis of chronic obstructive pulmonary disease: cellular and molecular mechanisms. *Cell Biochem Biophys.* 2005;43(1):167–188.
182. Postma DS, Kerkhof M, Boezen HM, Koppelman GH. Asthma and chronic obstructive pulmonary disease: common genes, common environments? *Am J Respir Crit Care Med.* 2011;183(12):1588–1594.
183. Castaldi PJ, Cho MH, Cohn M, et al. The COPD genetic association compendium: a comprehensive online database of COPD genetic associations. *Hum Mol Genet.* 2010;19(3):526–534.
184. He JQ, Ruan J, Connett JE, et al. Antioxidant gene polymorphisms and susceptibility to a rapid decline in lung function in smokers. *Am J Respir Crit Care Med.* 2002;166(3):323–328.

185. Liao N, Zhao H, Chen M-L, Xie Z-F. Association between the TGF- β 1 polymorphisms and chronic obstructive pulmonary disease: a meta-analysis. *Biosci Rep.* 2017;37(4):BSR20170747.
186. Ghio AJ, Hilborn ED, Stonehuerner JG, et al. Particulate matter in cigarette smoke alters iron homeostasis to produce a biological effect. *Am J Respir Crit Care Med.* 2008;178(11):1130–1138.
187. Najafinobar N, Venkatesan S, von Sydow L, et al. ToF-SIMS mediated analysis of human lung tissue reveals increased iron deposition in COPD (GOLD IV) patients. *Sci Rep.* 2019; 9(1):1–9.
188. Ziolkowska-Suchanek I, Mosor M, Gabryel P, et al. Susceptibility loci in lung cancer and COPD: association of IREB2 and FAM13A with pulmonary diseases. *Sci Rep.* 2015;5(1):1–14.
189. Zhou H, Yang J, Li D, et al. Association of IREB2 and CHRNA3/5 polymorphisms with COPD and COPD-related phenotypes in a Chinese Han population. *J Hum Genet.* 2012;57(11): 738–746.
190. Linden M, Rasmussen JB, Piitulainen E, et al. Airway inflammation in smokers with nonobstructive and obstructive chronic bronchitis. *Am Rev Respir Dis.* 1993;148(5):1226–1232.
191. Natarajan K, Gottipati KR, Berhane K, et al. Proteases and oxidant stress control organic dust induction of inflammatory gene expression in lung epithelial cells. *Respir Res.* 2016;17(1):137.
192. McGuinness AJA, Sapey E. Oxidative stress in COPD: sources, markers, and potential mechanisms. *J Clin Med.* 2017;6(2):21.
193. To M, Swallow EB, Akashi K, et al. Reduced HDAC2 in skeletal muscle of COPD patients. *Respir Res.* 2017;18(1):99.
194. Deslee G, Adair-Kirk TL, Betsuyaku T, et al. Cigarette smoke induces nucleic-acid oxidation in lung fibroblasts. *Am J Respir Cell Mol Biol.* 2010;43(5):576–584.
195. Deslee G, Woods JC, Moore C, et al. Oxidative damage to nucleic acids in severe emphysema. *Chest.* 2009;135(4):965–974.
196. Yao H, Arunachalam G, Hwang JW, et al. Extracellular superoxide dismutase protects against pulmonary emphysema by attenuating oxidative fragmentation of ECM. *Proc Natl Acad Sci U S A.* 2010;107(35):15571–15576.
197. Suki B, Bartolák-Suki E, Rocco PR. Elastase-induced lung emphysema models in mice. *Methods Mol Biol.* 2017;1639:67–75.
198. Rangasamy T, Cho CY, Thimmulappa RK, et al. Genetic ablation of Nrf2 enhances susceptibility to cigarette smoke-induced emphysema in mice. *J Clin Invest.* 2004;114(9):1248–1259.
199. Kong X, Cho MH, Anderson W, et al. Genome-wide association study identifies BICD1 as a susceptibility gene for emphysema. *Am J Respir Crit Care Med.* 2011;183(1):43–49.
200. Mercado N, Colley T, Baker JR, et al. Bicaudal D1 impairs autophagosome maturation in chronic obstructive pulmonary disease. *FASEB Bioadv.* 2019;1(11):688–705.
201. Barnes PJ, Baker J, Donnelly LE. Cellular senescence as a mechanism and target in chronic lung diseases. *Am J Respir Crit Care Med.* 2019;200(5):556–564.
202. Ito K, Barnes PJ. COPD as a disease of accelerated lung aging. *Chest.* 2009;135(1):173–180.
203. Maruyama N, Ishigami A, Kuramoto M, et al. Senescence marker protein-30 knockout mouse as an aging model. *Ann N Y Acad Sci.* 2004;1019(1):383–387.
204. Vogel H, Lim DS, Karsenty G, et al. Deletion of Ku86 causes early onset of senescence in mice. *Proc Natl Acad Sci U S A.* 1999;96(19):10770–10775.
205. Tsuji T, Aoshiba K, Nagai A. Alveolar cell senescence in patients with pulmonary emphysema. *Am J Respir Crit Care Med.* 2006;174(8):886–893.
206. Rutten EP, Gopal P, Wouters EF, et al. Various mechanistic pathways representing the aging process are altered in COPD. *Chest.* 2016;149(1):53–61.
207. Amsellem V, Gary-Bobo G, Marcos E, et al. Telomere dysfunction causes sustained inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2011;184(12):1358–1366.
208. Baker J, Vuppusetty C, Colley T, et al. Oxidative stress dependent microRNA-34a activation via PI3K α reduces the expression of sirtuin-1 and sirtuin-6 in epithelial cells. *Sci Rep.* 2016;6:35871.
209. Baker JR, Vuppusetty C, Colley T, et al. MicroRNA-570 is a novel regulator of cellular senescence and inflamming. *FASEB J.* 2019;33(2):1605–1616.
210. Kim V, Han MK, Vance GB, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. *Chest.* 2011;140(3):626–633.
211. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm Med.* 2011;11:36.
212. Guerra S, Sherrill DL, Venker C, et al. Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. *Thorax.* 2009;64(10):894–900.
213. Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *Eur Respir J.* 1995;8(8):1333–1338.
214. Levine SJ, Larivee P, Logun C, et al. Tumor necrosis factor-alpha induces mucin hypersecretion and MUC-2 gene expression by human airway epithelial cells. *Am J Respir Cell Mol Biol.* 1995;12(2):196–204.
215. Borchers MT, Carty MP, Leikauf GD. Regulation of human airway mucus by acrolein and inflammatory mediators. *Am J Physiol.* 1999;276(4):L549–L555.
216. Kohri K, Ueki IF, Nadel JA. Neutrophil elastase induces mucin production by ligand-dependent epidermal growth factor receptor activation. *Am J Physiol Lung Cell Mol Physiol.* 2002;283(3):L531–L540.
217. Casalino-Matsuda SM, Monzon ME, Conner GE, et al. Role of hyaluronan and reactive oxygen species in tissue kallikrein-mediated epidermal growth factor receptor activation in human airways. *J Biol Chem.* 2004;279(20):21606–21616.
218. Takeyama K, Dabbagh K, Jeong Shim J, et al. Oxidative stress causes mucin synthesis via transactivation of epidermal growth factor receptor: role of neutrophils. *J Immunol.* 2000;164(3):1546–1552.
219. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med.* 2010;363(23):2233–2247.
220. Janssen WJ, Stefanski AL, Bochner BS, Evans CM. Control of lung defence by mucins and macrophages: ancient defence mechanisms with modern functions. *Eur Respir J.* 2016;48(4):1201–1214.
221. Rowe SM, Jones I, Dransfield MT, et al. Efficacy and safety of the CFTR potentiator icenticaftor (QBW251) in COPD: results from a phase 2 randomized trial. *Int J Chron Obstruct Pulmon Dis.* 2020;15:2399–2409.
222. Allinson JP, Hardy R, Donaldson GC, et al. The presence of chronic mucus hypersecretion across adult life in relation to

- chronic obstructive pulmonary disease development. *Am J Respir Crit Care Med.* 2016;193(6):662–672.
223. Solomon GM, Fu L, Rowe SM, Collawn JF. The therapeutic potential of CFTR modulators for COPD and other airway diseases. *Curr Opin Pharmacol.* 2017;34:132–139.
224. Rojas DA, Iturra PA, Méndez A, et al. Increase in secreted airway mucins and partial Muc5b STAT6/FoxA2 regulation during *Pneumocystis* primary infection. *Sci Rep.* 2019;9(1):1–11.
225. Ramos FL, Krahne JS, Kim V. Clinical issues of mucus accumulation in COPD. *Int J Chron Obstruct Pulmon Dis.* 2014;9:139.
226. Singanayagam A, Glanville N, Girkin JL, et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. *Nat Comm.* 2018;9(1):1–16.
227. Lin VY, Kaza N, Birket SE, et al. Excess mucus viscosity and airway dehydration impact COPD airway clearance. *Eur Respir J.* 2020;55(1):1900419.
228. Hogg JC, Chu FS, Tan WC, et al. Survival after lung volume reduction in chronic obstructive pulmonary disease: insights from small airway pathology. *Am J Respir Crit Care Med.* 2007;176(5):454–459.
229. Goldring IP, Greenburg L, Ratner IM. On the production of emphysema in Syrian hamsters by aerosol inhalation of papain. *Arch Environ Health.* 1968;16(1):59–60.
230. Shapiro S. Proteinases in chronic obstructive pulmonary disease. *Biochem Soc Trans.* 2002;30(2):98–102.
231. Pierce RA, Mariani TJ, Senior R. Elastin in lung development and disease. *Ciba Found Symp.* 1995;192:199–212.
232. Shapiro S, Endicott S, Province M, et al. Marked longevity of human lung parenchymal elastic fibers deduced from prevalence of D-aspartate and nuclear weapons-related radiocarbon. *J Clin Invest.* 1991;87(5):1828–1834.
233. Fukuda Y, Masuda Y, Ishizaki M, et al. Morphogenesis of abnormal elastic fibers in lungs of patients with panacinar and centriacinar emphysema. *Hum Pathol.* 1989;20(7):652–659.
234. Eurlings IM, Dentener MA, Cleutjens JP, et al. Similar matrix alterations in alveolar and small airway walls of COPD patients. *BMC Pulm Med.* 2014;14(1):90.
235. Foronjy RF, Okada Y, Cole R, D'Armiento J. Progressive adult-onset emphysema in transgenic mice expressing human MMP-1 in the lung. *Am J Physiol Lung Cell Mol Physiol.* 2003;284(5):L727–L737.
236. Churg A, Zhou S, Wright JL. Matrix metalloproteinases in COPD. *Eur Respir J.* 2012;39:197–209.
237. Gharib SA, Manicone AM, Parks WC. Matrix metalloproteinases in emphysema. *Matrix Biol.* 2018;73:34–51.
238. Weathington NM, van Houwelingen AH, Noerager BD, et al. A novel peptide CXCR ligand derived from extracellular matrix degradation during airway inflammation. *Nat Med.* 2006;12(3):317–323.
239. Braber S, Koelink PJ, Henricks PA, et al. Cigarette smoke-induced lung emphysema in mice is associated with prolyl endopeptidase, an enzyme involved in collagen breakdown. *Am J Physiol Lung Cell Mol Physiol.* 2011;300(2):L255–L265.
240. van Houwelingen AH, Weathington NM, Verweij V, et al. Induction of lung emphysema is prevented by L-arginine-threonine-arginine. *FASEB J.* 2008;22(9):3403–3408.

CHAPTER 39

Chronic Obstructive Pulmonary Disease and α 1-Antitrypsin Deficiency

Darrell N. Kotton

Andrew A. Wilson

INTRODUCTION

While predisposition to COPD is widely known to have a significant genetic basis,¹ the only known monogenic cause is the genetic mutation that results in α -1 antitrypsin deficiency (AATD). AATD was first identified in 1963 by Laurell and Eriksson, who initially described a cohort of five individuals lacking the α 1 globulin fraction, as revealed with serum protein electrophoresis. Three of the five suffered from significant pulmonary disease.² Subsequently, AATD was shown to result from the homozygous inheritance of a single base-pair mutation in the *SERPINA1* gene, which encodes α 1-antitrypsin protein.

Misfolded AAT proteins are poorly secreted and functionally abnormal—features that collectively predispose affected individuals to developing panlobular emphysema and COPD. While the prevalence in the population is not precisely known, AATD is estimated to afflict approximately 100,000 individuals in the United States and to account for approximately 1% to 4.5% of cases of COPD.^{3–7} Coupled with the observation that the cysteine protease inhibitor papain induces emphysema in rats when instilled intratracheally,⁸ the discovery of AATD and its association with emphysema led to the formation of the protease/antiprotease hypothesis as a basis for the pathogenesis of COPD (emphysema).

EPIDEMIOLOGY

The Z mutation is believed to have arisen from a single origin approximately 2000 years ago, potentially in the Viking population,^{9,10} who then disseminated it in southern Scandinavia. Studies of gene frequency have demonstrated significant variance among European nations, in which a gradient of gene frequency has been found, including high levels in the Northwest that decrease toward the Southeast.¹⁰ In Europe, the highest levels are found in regions of Estonia, Latvia, Sweden, France, Ireland, southern England, and northern Spain.¹⁰ Outside of Europe, the Z mutation is found at high levels in countries where it was introduced by European migration, including the United States, Australia, and New Zealand.^{9,11} Z gene frequency varies across African nations, but, on average, is approximately half of that seen in the United States; the frequency is significantly lower in other parts of the world, including China, South Korea, and Japan.^{11,12}

The overall prevalence of the Pi^{*}ZZ phenotype has been estimated from population-based studies. A screening study of 200,000 newborns in Sweden in 1972–1974 demonstrated a prevalence of 1 in 1600 newborns.¹³ Studies in U.S. populations have estimated a prevalence ranging from 1 in 2857 to 1 in 5097.^{14–16} Based on sampling of limited numbers of patients, the Pi^{*}ZZ phenotype is estimated to account for 1% to 4.5% of cases of COPD in the United States.^{3,4,6,7}

PATHOPHYSIOLOGY

Mechanisms responsible for the development of lung or liver disease resulting from AATD have been extensively studied (Fig. 39-1), and an understanding of these mechanisms continues to evolve as modern molecular methods and animal models of disease improve.^{17–19}

Liver hepatocytes express and secrete the highest levels of α 1-antitrypsin protein and, consequently, are the predominant source of circulating AAT. As the name of the protein implies, AAT functions as a serine protease inhibitor (serpin) with numerous antiprotease activities, including antitrypsin and antineutrophil elastase functions.^{17,20,21} AAT is found in nearly all body fluids, including saliva, tears, breast milk, urine, and semen, with concentrations in bronchoalveolar lavage fluid reaching approximately 10% of those in the circulation.^{22–26} Since AAT is found in lung tissue and is considered the major antielastase of the lower respiratory tract, these observations serve as the foundation of the hypothesis that secreted AAT from hepatocytes circulates to lung tissue, where its primary function is to protect lung matrix molecules, such as elastin, from degradation by unrestrained local leukocyte-derived proteases and elastases.^{19,20,27} Deficient AAT circulating levels or incomplete antiprotease activity is postulated to result in protease–antiprotease imbalance in the lung and degradation of lung elastin over time due to overexuberant activity of elastase and other serine proteases.²⁷ In patients with cirrhosis due to AATD who receive liver transplantation from a normal (PiMM) donor, circulating levels of AAT are normalized,²⁸ consistent with hepatocytes serving as the predominant source of circulating AAT.

Multiple mechanisms in AAT-deficient individuals are responsible for both the abnormally low circulating blood levels of AAT and diminished antiprotease activity; each type of AAT mutation contributes uniquely to one or both perturbations. Mutant Z-AAT protein has been most extensively studied using patient specimens, heterologous cell lines engineered to express a cDNA encoding the human Z mutant protein, or a variety of animal models.^{29–34} These studies reveal that in contrast to the normal M-AAT, which is translated and secreted as a protein monomer, Z mutant protein displays posttranslational misfolding, intracellular mistrafficking, delayed protein processing, and polymerization with other Z mutant protein polypeptides, resulting in intracellular accumulation and significantly diminished and delayed extracellular secretion.^{19,34–38} The intracellular accumulation of polymerized Z protein in hepatocytes results in activation of a variety of cellular stress pathways, including ER stress, leading to hepatotoxicity and increased risk of neonatal jaundice, juvenile cirrhosis, or adult cirrhosis that is well described in individuals with PiZZ AATD.^{37,39} Further exacerbating the diminished antiprotease activity that results from low levels of secreted AAT, the Z mutation also compromises the antiprotease activity of the protein itself.¹⁹

It is well accepted that two Z alleles result in highly polymeric AAT polypeptides, and recent reports suggest polymerization can also occur extracellularly with detectable polymers, derived from the liver, found circulating in the blood stream, or deposited in nonhepatic tissues of individuals with PiZZ AATD.⁴⁰ Less common AATD mutations (such as PiS) do not appear to be polymeric and, thus, are associated with less risk of liver disease. The presence of a single Z allele (e.g., PiMZ or PiSZ) has been shown sufficient to form polymeric AAT protein,⁴⁰ and it is well established that all genotypes with a single Z allele exhibit lower circulating serum levels due to diminished hepatic secretion.^{18,19,38,41,42}

Accumulating studies in recent years have added complexity to the original and relatively simple hypothesis that COPD pathogenesis in the setting of AATD is due solely to protease–antiprotease imbalance resulting from low and ineffective levels of hepatocyte-derived

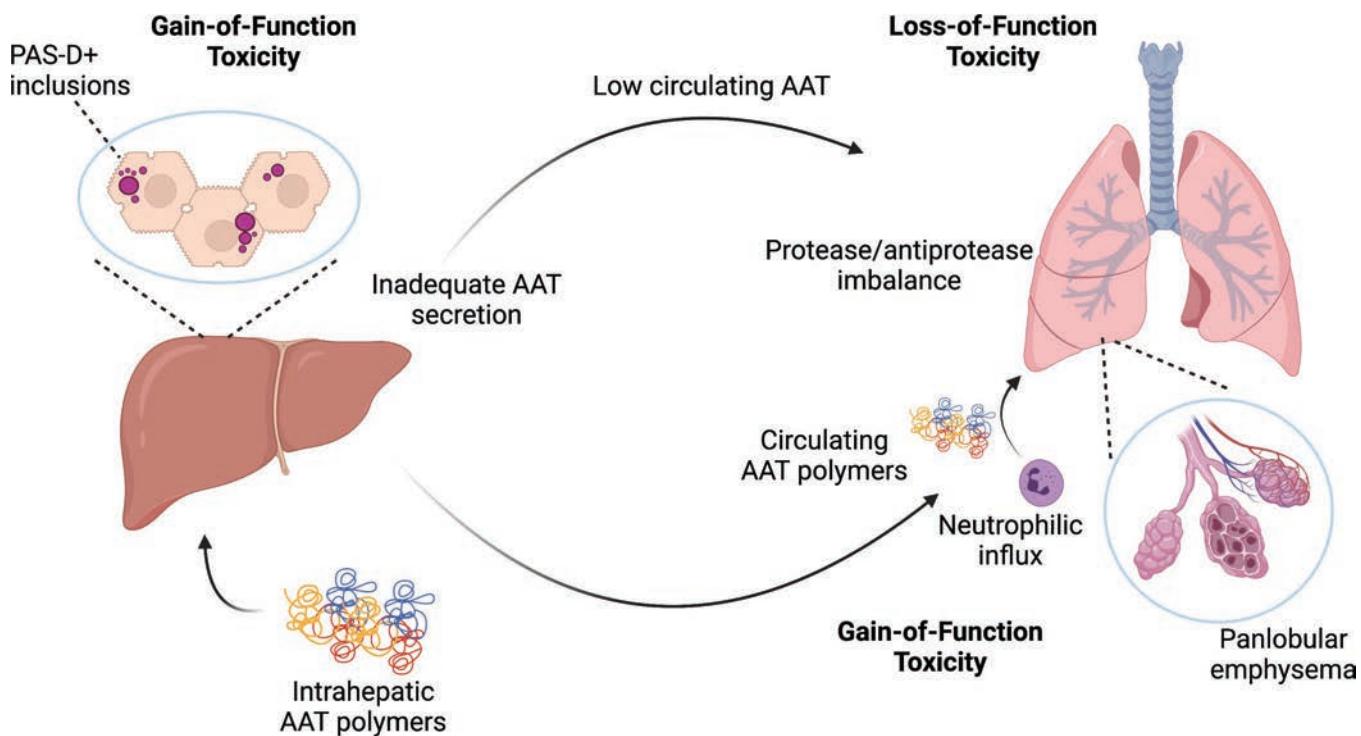


Figure 39-1 Pathophysiology of liver and lung disease in AATD. Misfolded Z-AAT protein forms polymers in the endoplasmic reticulum of hepatocytes, causing injury through a gain-of-toxic-function mechanism. Intrahepatic inclusions of polymerized Z-AAT protein stain positive with periodic acid-Schiff stain but are resistant to digestion with diastase (PAS-D). Poor hepatic Z-AAT secretion leads to low circulating

circulating AAT protein. In addition to its primary role in protease inactivation, numerous investigations demonstrate that AAT exerts both anti-inflammatory and immunomodulatory effects in a variety of conditions and cell types—in some cases, independent of its antiprotease activity.^{43–46} Both loss of normal M-AAT anti-inflammatory activity,⁴³ and gain of pro-inflammatory activities resulting from the presence of Z mutant polymeric protein deposits in tissues, combine to activate potentially destructive lung inflammation.^{40,47} Effects on activation and trafficking of multiple immune cell types have been documented, including neutrophils,⁴⁸ mast cells,⁴⁹ macrophages,⁵⁰ and T cells.⁵¹

Additional studies further support anti-inflammatory and anti-apoptotic effects of normal M-AAT protein. Reports of organ ischemia or cigarette smoke exposure have demonstrated attenuation of neutrophilic infiltration of the kidney, liver, and lung,^{52–55} as well as reduction in cell death due to simulated myocardial infarction⁵⁶ in the setting of supplementation with exogenous AAT. Collectively, these studies have demonstrated direct antiapoptotic effects of AAT, as well as inhibition of caspases^{54,57,58} and anti-inflammatory effects characterized by attenuation of increases in local or systemic TNF- α . Similarly, in animal lung transplant models, treatment with AAT reduced ischemic-reperfusion injury by inhibiting neutrophilic infiltration of the lung, together with reductions in cytokines, including IL-1 α , IL-4, IL-12p70, MCP-1, and TNF- α .^{44,59}

In contrast to the anti-inflammatory activity of normal M-AAT, the polymeric form of Z mutant AAT is proinflammatory, resulting in cellular toxicity, leukocyte activation, and cytokine release.^{60,61} Studies using animals engineered to overexpress human Z protein have found evidence of cellular toxicity or intracellular proteostatic effects in non-hepatic tissues including the lung.^{43,62,63} For example, lung epithelial ER stress and dysregulation of autophagy have been found in PiZ

and tissue AAT levels. Z-AAT polymers in the circulation and lung interstitium are chemoattractant for neutrophils, which are found at increased levels in the lung of PIZZ patients. Together, gain-of-function and loss-of-function mechanisms contribute to an imbalance of protease and antiprotease activity in the lung leading to tissue damage and emphysema.

transgenic mice.⁶⁴ These observations have raised the possibility that misfolded, polymeric AAT protein might also cause toxic gain-of-function effects in lung tissue, as has been established in hepatocytes. In the setting of true null mutations, no AAT protein is produced by the liver or any other lineage. Therefore, elevated COPD risk, without hepatotoxicity, is thought to result solely from low circulating AAT levels and diminished lung antiprotease activity.⁶⁵

Further complicating matters, an increasing number of cell lineages are now recognized as expressing and possibly secreting AAT. While hepatocytes are the main source of circulating AAT, approximately 20% of the total is produced by other AAT-producing cell types—a list that includes monocytes and macrophages, in addition to epithelial cells of the lung, kidney, intestine, pancreas, thymus, adrenal gland, ovary, testis, and corneum.^{66–73} The function of normal AAT in these lineages remains poorly understood, but a nascent literature implicates some of these alternate lineages as contributing to disease pathogenesis in AATD settings, for example, through activation of leukocytes.^{74,75} Mobilization of bone marrow-derived hematopoietic populations also may be impacted as a result of AATD, since mouse models indicate that local bone marrow AAT functions to precisely regulate proteolytic release of tethered hematopoietic progenitors from their bone marrow niche.⁷⁶ It remains unclear, however, whether AAT activity in the bone marrow plays any role in AATD-related lung disease.

In summary, a broad published literature and clinical observations indicate that loss-of-function AAT mutations contribute to COPD pathogenesis in patients with AATD. For example, patients with rare null mutations are at significantly increased risk of developing COPD,⁶⁵ and mice engineered through gene editing to have deletions in AAT-encoding genes are significantly more susceptible to spontaneous (age-related) or smoke-induced emphysema.⁷⁷ More recent

and still evolving literature also suggests that beyond simple loss of function, a subset of mutant AAT proteins, such as Z-AAT, likely also contributes to pathogenesis of COPD through toxic gain-of-function mutations involving protein misfolding, accumulating of polymers, and a variety of potential inflammatory and cytotoxic mechanisms.

CLINICAL MANIFESTATIONS

Patients with AATD-associated COPD present with symptoms that mirror those of the non-AATD population with COPD, including progressive dyspnea, hypoxemia, cough productive of sputum, and wheeze in the context of viral respiratory infection.⁷⁸ These similarities can make it challenging to distinguish the two populations. A typical patient with AATD experiences respiratory symptoms for years and seeks evaluation by multiple physicians prior to the diagnosis of AATD.^{79,80} Early onset of symptoms in the fourth or fifth decade of life and disease out of proportion to exposure history are common historic characteristics of patients with AATD-associated COPD.^{33,81} Features of the family history can be suggestive; a history revealing multiple family members with diagnoses of liver disease or COPD should increase suspicion.

Classically, patients with AATD-associated COPD manifest panlobular, lower-lobe emphysema, distinct from the upper-lobe-predominant, centrilobular emphysema typical of non-AATD COPD.^{82,83} However, a variety of other clinical and radiographic presentations are common among patients with AATD-associated COPD. Case series reviewing radiographic patterns of PiZZ AATD-associated disease found that only 20% of plain chest x-rays⁸² and 64% of chest CT scans⁸⁴ exhibited a basilar distribution of emphysema. Reliance on this classic radiographic presentation as the basis for testing to diagnose AATD is, therefore, insensitive and misses a large proportion of affected individuals.⁸⁵

Aside from emphysema, bronchiectasis is the most common radiographic abnormality observed in PiZZ AATD. Reported frequency of clinically significant bronchiectasis is variable in the literature and ranges from as low as 2% of 1129 participants in the NHLBI registry to as high as 27% of 74 study participants whose lung disease was characterized by CT scan.⁸⁶ Although speculative, it seems likely that the increased clinical use of cross-sectional imaging, combined with increasing resolution capabilities of CT scanners, results in increased detection of bronchiectasis in PiZZ AATD.

Patients with PiZZ AATD commonly experience a progressive decline in FEV₁ that can occur at a rate faster than in individuals with non-AATD-associated COPD. Aggregate data from several large longitudinal cohort studies suggest a mean decline in FEV₁ of 41 to 86 mL/year among PiZZ former or never former smokers.⁸⁷⁻⁸⁹ This decline was higher at 70 to 132 mL/year for current smokers in the same studies, consistent with exquisite sensitivity of PiZZ individuals to cigarette smoke injury. The value of smoking cessation in this population is supported by data from the Danish AAT Deficiency Registry, in which FEV₁ decline among those who quit smoking during the study period was measured at 58 mL/year compared with 132 mL/year among those who continued to smoke.⁸⁹ Predictors of accelerated FEV₁ decline among individuals with the PiZZ genotype include male sex, age range 30 to 44 years, active smoking, bronchodilator responsiveness, and mean predicted FEV₁ of 35% to 79%. Occupational or environmental exposure to pollutants also have been identified as risk factors for accelerated lung function decline.^{90,91}

Aside from lung disease, the primary organ affected in AATD is the liver, where injury manifests either as jaundice among neonates, or as fibrosis in adults; a subset progress to cirrhotic liver disease. Neutrophilic panniculitis, seen in fewer than 1% of Pi*ZZ patients, can cause erythematous, tender subcutaneous nodules.⁹² Other conditions associated with AATD include ANCA-associated vasculitis,⁹³ glomerulonephritis,⁹⁴ and chronic kidney disease.⁹⁵

NATURAL HISTORY AND PROGNOSIS

Data from the Swedish National Registry provide insight into the longevity of individuals with PiZZ. Of 568 PiZZ never-smokers followed in this cohort, 93 had died at the time of analysis, with a median age of death of 76 years,⁹⁶ consistent with a relatively normal life expectancy. Within this never-smoking population, a higher mortality rate was observed among individuals in whom AATD was identified on the basis of respiratory symptoms than in those identified through screening, whose mortality rate was similar to that of the general population. Of these 93 participants, the underlying cause of death was identified as emphysema in 42 (45%), despite their status as never-smokers, whereas 26 (28%) died due to complications of liver disease. These findings differ to a degree from those observed in the NHLBI registry, in which 72% of deaths among 204 decedents, of whom only 16 were never-smokers, resulted from emphysema and associated respiratory failure compared to 10% from cirrhosis.⁹⁷ A third study of Swedish PiZZ adults identified respiratory failure as the primary cause of death in approximately 60% of 91 deaths, with liver disease accounting for 13%.⁹⁸ Mortality rates are not equally distributed among all those with PiZZ and are higher among smokers,⁹⁹ those with lower FEV₁,^{97,100} and those identified on the basis of respiratory symptoms.⁹⁹

Among patients with Pi*ZZ AATD, the risk of developing emphysema is quite high, although the precise risk is unknown. Of 42 NHLBI registry participants with lung tissue available for review following either autopsy or lung transplant, 100% were found to have emphysema.¹⁰¹ In another study, 119 consecutive Pi*ZZ patients were evaluated in clinical practice; 17 (14%) did not have significant emphysema based on CT densitometry measurements,⁸⁴ consistent with the concept that a subset of Pi*ZZ individuals might not be afflicted. Notably, however, the mean age of these 17 individuals was only 44 years, leaving open the possibility that they eventually might develop disease.

The relative risk of Pi*Z heterozygotes, who represent a considerable percentage of the U.S. Caucasian population, has historically been uncertain. Pi* SZ heterozygotes, in particular, were previously thought to be at increased risk of lung damage and were routinely offered augmentation therapy in the United States. Emerging data, however, suggest otherwise. Franciosi et al., in a prospective, observational, family-based study, reported no differences in either spirometry or symptom scores between non-index case, never-smoker individuals with Pi*SZ, and family member controls with Pi*MM or Pi*MS.¹⁰² Zero of 19 Pi*SZ never-smokers in this study were found to have CT-based emphysema, suggesting that a single Z allele does not commonly cause disease in the absence of an environmental insult. Cigarette smoking was associated with worse spirometric outcomes in Pi*SZ ever-smokers relative to controls, although smoking cessation appeared to attenuate the accelerated decline. Intriguingly, emphysema in Pi*SZ ever-smokers was noted to occur in an upper-lobe distribution, suggesting a pathophysiology distinct from Pi*ZZ AATD.

Additional data paint a similar picture for Pi*MZ heterozygotes. A family-based, prospective observational study by the investigators who authored the PI*SZ study described above found no differences between never-smoker, non-index Pi*MZs, and Pi*MM controls. Among ever-smokers matched for either high (>20 pack-years) or low (<20 pack-years) levels of smoke exposure, Pi*MZs had worse spirometric outcomes relative to controls.¹⁰³ Pi*MZ heterozygosity was associated with an adjusted odds ratio for COPD of 5.18. Additional data derived from 1693 non-Hispanic, white participants of the SPIROMICS cohort (all 40–80 years old with a ≥20-pack-year smoking history) demonstrated that white Pi*MZ heterozygotes had lower lung function, worse spirometric obstruction, and more CT-based emphysema than white Pi*MMs.¹⁰⁴

In aggregate, the literature suggests that among ever-smokers, Pi*Z heterozygotes as a group are at increased risk of lung disease

compared with Pi^{*}MM individuals, consistent with a gene × environment interaction in which ongoing environmental exposure is necessary to induce disease.

DIAGNOSIS

Current clinical guidelines recommend one-time testing of all patients with persistent spirometric airflow obstruction, regardless of age or disease severity.^{105–107} In addition to COPD, respiratory presentations that should prompt consideration of testing for AATD include emphysema in the absence of airflow obstruction and a family history of lung or liver disease.

Laboratory testing to diagnose AATD includes evaluation of levels of AAT protein in the serum, identification of AAT protein variants, or testing for variant gene sequences.

Serum AAT levels, most commonly measured by nephelometry, quantify the amount of AAT protein in the serum. A threshold level of 24.4 μM/L (110 mg/dL) distinguishes Pi^{*}MM proteins from protein combinations including at least one S or Z with 73.4% sensitivity and 88.5% specificity.¹⁰⁸ However, because a variety of AAT allele combinations can result in serum AAT ranges with significant overlap, testing for serum AAT levels in isolation frequently does not allow one to infer the patient's phenotype/genotype. Since AAT is a known acute-phase reactant, with serum levels rising in the setting of systemic inflammation, interpretation of testing based solely on serum levels may be limited, particularly if these tests are performed in the setting of active infections or other inflammatory insults.^{109,110}

Protein phenotyping to identify specific AAT variant proteins based on their migration pattern by isoelectric focusing can be a useful modality to diagnose or exclude AATD. Phenotyping can be used to identify rare variants that might be missed by PCR-based genotyping. However, the technique can be challenging to interpret in the context of null alleles or alleles that generate similar migration patterns (e.g., M-like alleles may produce a protein pattern similar to M protein).¹¹¹

Detection of gene variants that encode deficient AAT proteins is an increasingly employed testing approach. Most commonly, targeted genotyping using PCR or RFLP analysis is performed to test for the normal M allele, together with a panel of common pathogenic variants. Rare alleles are generally not tested for and, therefore, are not detected using this approach. Gene sequencing, capable of identifying null alleles and other rare variants, can be a useful adjunct modality and is most commonly applied when the clinical presentation, reported AAT level, and genotype or phenotype are incongruent.¹¹¹

Physician practice has lagged behind screening guidelines recommending the testing of all patients with obstructive lung disease^{80,112} for AATD. This fact, together with the large size of the screenable population, suggests the need for an approach that maximizes cost effectiveness. A variety of testing algorithms have been evaluated with this goal in mind.¹¹¹ Common screening approaches outlined include testing of AAT levels, either alone or in combination with targeted genotyping. Protein phenotyping and DNA sequencing in these reports were subsequently applied if AAT levels were found to be low or if Z or S alleles were identified by genotyping.

MANAGEMENT

Medical management of AATD-related COPD is similar to management of other forms of COPD,¹⁰⁵ including a focus on avoidance of smoke exposure, treatment of hypoxemia, use of inhaled bronchodilators and inhaled glucocorticoids, referral for pulmonary rehabilitation, consideration of lung transplantation in those with severe COPD, and adherence to standard vaccine guidelines (Chapter 40). A significant difference from usual COPD management is consideration of genetic counseling and screening of family members

for inherited AATD, as well as specific attention to the deficiency in circulating AAT in those with declining lung function.^{19,105} An attempt to correct the hypothesized protease–antiprotease imbalance associated with deficient AAT levels and declining lung function forms the basis of the predominant treatment approach specific for AATD-associated COPD, so-called augmentation therapy. With augmentation therapy, levels of circulating AAT and antiprotease activities are augmented through regular intravenous infusions of normal (M) AAT protein purified from pooled human plasma specimens.^{105,113}

Secreted AAT protein circulates with an average concentration of 150 to 300 mg/dL in blood plasma and a half-life of approximately 5 days.^{20,37,114} In the most common deficiency state, PiZZ, circulating AAT levels are reduced to 10% to 15% of normal.³⁷ Several dosing approaches have been pursued in an effort to augment circulating levels in those with progressive loss of lung function due to AATD. Clinical trials have demonstrated variable results.^{105,107,113,115–126}

Rather than normalizing circulating levels, the goal of augmentation therapy is to increase deficient levels to a concentration above a protective threshold. Those with treatment criteria, including severely deficient circulating AAT levels (serum levels <11 μmol/L or <57 mg/dL) and evidence of airflow obstruction, qualify for the U.S. Food and Drug Administration (FDA)-approved treatment regimen of weekly intravenous infusions of pooled human plasma-derived AAT at a dose of 60 mg/kg body weight.¹⁰⁵ The global initiative for COPD (GOLD) guidelines suggest patients with AATD with an FEV₁ of 35% to 65% of normal qualify for augmentation therapy,¹²⁷ whereas American Thoracic Society guidelines indicate that patients with AATD and an FEV₁ <80% are suitable candidates.² Some guidelines suggest evidence of emphysema on CT scan also should prompt consideration for augmentation therapy for AATD.¹⁰⁵

Data in support of the clinical efficacy of augmentation therapy include randomized clinical trials, as well as longitudinal cohort follow-up studies, registry analyses, and meta-analyses focusing on outcomes such as AAT serum levels, lung function, and lung density on CT; mortality data are more limited.^{105,107,113,115–126} For example, a systematic review and meta-analysis performed on data from trials performed prior to 2009 that included a cumulative total of 1509 patients concluded that augmentation therapy slowed FEV₁ decline in COPD; those with moderate airflow obstruction appeared to benefit most.¹²⁸

In a randomized, double-blind, placebo-controlled trial of intravenous augmentation treatment in severe α1-antitrypsin deficiency (RAPID), rates of CT lung density decline were compared between 93 individuals on augmentation therapy versus 87 receiving placebo.¹¹⁵ There was no statistically significant difference in the co-primary endpoint of CT density assessed at both FRC and TLC combined; however, there was significantly less annual decline in lung density in the treatment group based on CT densitometry measured at TLC, lending support to the conclusion that augmentation therapy slows the progression of emphysema in individuals with severe AATD.

In an open-label extension of the same trial (RAPID-OLE), the long-term efficacy and safety of augmentation therapy for emphysema caused by severe AATD was reported based on continued treatment of 76 participants from the original treatment group (early start group) and 64 participants from the placebo group (late start group with therapy delayed by 2 years compared with the early group).¹²⁹ The rate of lung density loss was less in the early-start treatment group. Furthermore, the rate of loss in the delayed treatment group slowed after the initiation of delayed therapy, although previously lost lung density was never recovered.

Support for the clinical efficacy of augmentation therapy is also provided by additional observational studies that suggested beneficial effects on survival and lung function. For example, a

retrospective analysis of NHLBI's Alpha-1 Antitrypsin Deficiency Registry found that augmentation therapy improves survival in severely deficient patients with predicted FEV₁ between 10% and 60%.¹¹⁸ Another study also found a significantly reduced rate of FEV₁ decline in a German cohort of former smokers with AATD receiving augmentation therapy compared with a Danish cohort of former smokers who did not receive therapy over a 3.2-year average follow-up period.¹²³ Finally, an additional study comparing rates of decline in FEV₁ in individuals followed longitudinally before and after they began augmentation therapy concluded that treatment significantly slowed the loss of FEV₁ in severe AATD.¹³⁰

While the majority of studies finding beneficial efficacy involve the FDA-approved standard weekly intravenous dosing of 60 mg/kg pooled human plasma-derived AAT, alternative regimens, such as increased time intervals or increased dosing regimens, have been reported.^{113,117,121} Based on a recent pilot study,¹¹⁷ doubling the dose of augmentation therapy was found to be safe and to have potentially more anti-inflammatory effects; effects on clinical efficacy were indeterminate.

The optimal timing of initiating augmentation therapy also has been debated, with compelling arguments made for the use of CT scans to detect loss of lung function in patients with AATD earlier than would be discovered by physiologic testing or chest radiographs. Presumably, augmentation therapy would be started prior to significant and irretrievable loss of lung function.¹¹³

Whether augmentation therapy reduces COPD exacerbation events remains uncertain, based on mixed results from clinical trials, such as the RAPID trial,¹¹⁵ which found no reduction in exacerbation rates; other studies found augmentation therapy was associated with reduced exacerbations.¹³¹ Acute exacerbations of AATD-related COPD have been reported by some to differ from usual COPD exacerbations, as evidenced by greater frequency and duration of symptoms;¹³² however, the extent and consequence of this is not known. Accordingly, conventional COPD treatments are used to treat exacerbations in patients with AATD, despite a paucity of evidence evaluating their efficacy.¹³²

As with other forms of severe COPD, referral for lung transplant evaluation should be pursued in those with AATD-related severe and progressive COPD. Posttransplant survival has been studied in recipients with AATD compared to other forms of COPD¹³³ and was found to be similar, at least in the era since the use of lung allocation scores. In addition, a longitudinal study of patients with COPD following lung transplant¹³⁴ found that posttransplant FEV₁ over time, severity of acute rejection, and survival were similar overall in patients with AATD compared with AAT-replete patients. A notable exception were those who received double lung transplants, where FEV₁ declined faster in those with AATD, suggesting that further studies may be needed to compare outcomes in those with AATD receiving single versus double lung transplants.

Some studies have attempted to determine whether there is a beneficial role for augmentation therapy post-lung transplantation in AATD transplant recipients,^{135,136} but efficacy of this approach remains uncertain. Since several decades typically elapse before loss of lung function is clinically significant in PiZZ AATD individuals, it remains speculative as to whether prolonged, transient, or episodic augmentation therapy post-lung transplantation is indicated to preserve function of the new graft in AATD transplant recipients. Thus, augmentation therapy is not currently routinely prescribed post-lung transplantation, since it is costly and lacks proven efficacy; furthermore, decisions regarding continuation versus cessation of augmentation therapy post-transplant are individualized and based on expert consultation, given the paucity of available data.

A number of emerging therapeutic options using novel technologies are being actively pursued for potential future use in patients with AATD.^{137,138}

Inhaled augmentation therapy has been evaluated in several clinical trials, but clinical efficacy remains uncertain to date.^{139–142}

Numerous gene therapy trials have been attempted to correct the loss of function associated with the most frequent mutations responsible for AATD.¹⁴³ In mouse models, adeno-associated virus (AAV)-based vectors for episomal overexpression of human cDNA encoding M-AAT have been successfully deployed by in vivo injection or infusion to liver hepatocytes or large muscle beds, resulting in prolonged in vivo secretion into the circulation from cells in the transfected target tissue.^{144–148}

Additional proof-of-concept studies using intratracheally delivered local lentiviral overexpression in resident alveolar macrophages in mouse lungs have resulted in secretion of M-AAT into the lung epithelial lining fluid in vivo, ameliorating elastase-induced emphysema in mice.³²

Despite the promise of gene therapy tests in animal models, in human clinical trials intramuscular injections of AAV vectors have resulted only in low circulating M-AAT levels, far below the therapeutic threshold thought to be needed for efficacy in patients.^{144,149,150} Newer AAV-based vectors or RNA interfering molecules have been designed to knock down expression of mutant Z-AAT in liver hepatocytes while either overexpressing M-AAT cDNA from the same hepatocytes or replacing circulating M-AAT with intravenous augmentation therapy.¹⁴⁵ These emerging therapies are being studied in ongoing or planned clinical trials,¹⁵¹ but to date, gene and RNAi based therapies for AATD remain experimental.

With the recent emergence of gene editing technologies, such as zinc finger nucleases, TALENs, or CRISPR, the possibility of correcting AAT gene mutations to normal in the endogenous AAT gene locus in patient-specific cells has been demonstrated.¹³⁷ Induced pluripotent stem cells have been generated from patients with AATD,^{152–155} and successful gene editing of these cells from Z to M genotypes has been demonstrated, followed by in vitro differentiation of the corrected stem cells into hepatocytes for transplantation into animal models.¹³⁷ More recently, in vivo gene editing of AAT encoding loci in vivo in mouse livers has been successfully demonstrated.¹⁵⁶ These new and emerging proof-of-concept animal studies provide hope that innovative and potentially curative gene editing strategies to correct AATD in humans may be feasible in the future.¹³⁸

REFERENCES

1. Sakornsakopat P, Prokopenko D, Lamontagne M, et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. *Nat Genet*. 2019;1–17.
2. Laurell CB, Eriksson S. The electrophoretic α 1-globulin pattern of serum in α 1-antitrypsin deficiency. 1963. *COPD*. 2013;10(Suppl 1):3–8.
3. Fagerhol MK, Hauge HE. Serum Pi types in patients with pulmonary diseases. *Acta Allergol*. 1969;24(2):107–114.
4. Kueppers F, Fallat R, Larson RK. Obstructive lung disease and α 1-antitrypsin deficiency gene heterozygosity. *Science*. 1969;165(3896):899–901.
5. Kueppers F, Miller RD, Gordon H, et al. Familial prevalence of chronic obstructive pulmonary disease in a matched pair study. *Am J Med*. 1977;63(3):336–342.
6. Lieberman J, Winter B, Sastre A. Alpha 1-antitrypsin Pi-types in 965 COPD patients. *Chest*. 1986;89(3):370–373.
7. Cox DW, Hoepfner VH, Levison H. Protease inhibitors in patients with chronic obstructive pulmonary disease: the alpha1-antitrypsin heterozygote controversy. *Am Rev Respir Dis*. 2015;113(5):601–606.

8. Gross P, Babyak MA, Tolker E, Kaschak M. Enzymatically produced pulmonary emphysema; a preliminary report. *J Occup Med.* 1964;6:481–484.
9. Lomas DA. The selective advantage of $\alpha 1$ -antitrypsin deficiency. *Am J Respir Crit Care Med.* 2006;173(10):1072–1077.
10. Blanco I, Fernández E, Bustillo E. Alpha-1-antitrypsin PI phenotypes S and Z in Europe: an analysis of the published surveys. *Clin Genet.* 2001;60(1):31–41.
11. Janciauskiene SM, Bals R, Koczulla R, et al. The discovery of $\alpha 1$ -antitrypsin and its role in health and disease. *Respir Med.* 2011;105(8):1129–1139.
12. de Serres FJ. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: summary of an analysis of published genetic epidemiologic surveys. *Chest.* 2002;122(5):1818–1829.
13. Sveger T. $\alpha 1$ -antitrypsin deficiency in early childhood. *Pediatrics.* 1978;62(1):22–25.
14. Colp C, Pappas J, Moran D, Liebemuin J. Variants of $\alpha 1$ -antitrypsin in Puerto Rican children with asthma. *Chest.* 1993;103(3):812–815.
15. O'Brien ML, Buist NRM, Murphrey WH. Neonatal screening for alpha1-antitrypsin deficiency. *J Pediatrics.* 1978;92(6):1006–1010.
16. Silverman EK, Miletich JP, Pierce JA, et al. Alpha-1-antitrypsin deficiency. High prevalence in the St. Louis area determined by direct population screening. *Am Rev Respir Dis.* 1989;140(4):961–966.
17. Stoller JK, Aboussouan LS. A review of 1-antitrypsin deficiency. *Am J Respir Crit Care Med.* 2012;185(3):246–259.
18. Gooptu B, Ekeowa UI, Lomas DA. Mechanisms of emphysema in 1-antitrypsin deficiency: molecular and cellular insights. *Eur Respir J.* 2009;34(2):475–488.
19. Strnad P, McElvaney NG, Lomas DA. Alpha 1-antitrypsin deficiency. *N Engl J Med.* 2020;382(15):1443–1455.
20. Perlmutter D, Pierce JA. The alpha 1-antitrypsin gene and emphysema. *Am J Physiol.* 1989;257(4):L147–L162.
21. Ekeowa UI, Gooptu B, Belorgey D, et al. $\alpha 1$ -Antitrypsin deficiency, chronic obstructive pulmonary disease and the serpinopathies. *Clin Sci (Lond).* 2009;116(12):837–850.
22. Society AT, Society ER. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med.* 2003;168(7):818–900.
23. Berman MB, Barber JC, Talamo RC, Langley CE. Corneal ulceration and the serum antiproteases. I. Alpha 1-antitrypsin. *Investigative Ophthalmology.* 1973;12(10):759–770.
24. Chowanadisai W, Lönnadal B. Alpha(1)-antitrypsin and antichymotrypsin in human milk: origin, concentrations, and stability. *Am J Clin Nutr.* 2002;76(4):828–833.
25. Poortmans J, Jeanloz RW. Quantitative immunological determination of 12 plasma proteins excreted in human urine collected before and after exercise. *J Clin Invest.* 1968;47(2):386–393.
26. Janciauskiene S. Conformational properties of serine proteinase inhibitors (serpins) confer multiple pathophysiological roles. *Biochim Biophys Acta.* 2001;1535(3):221–235.
27. Gadek JE, Fells GA, Zimmerman RL, et al. Antielastases of the human alveolar structures. Implications for the protease-antiprotease theory of emphysema. *J Clin Invest.* 2016;68(4):889–898.
28. Carey EJ, Iyer VN, Nelson DR, et al. Outcomes for recipients of liver transplantation for alpha-1-antitrypsin deficiency-related cirrhosis. *Liver Transpl.* 2013;19(12):1370–1376.
29. Long OS, Benson JA, Kwak JH, et al. A *C. elegans* model of human $\alpha 1$ -antitrypsin deficiency links components of the RNAi pathway to misfolded protein turnover. *Hum Mol Genet.* 2014;23(19):5109–5122.
30. Haddock CJ, Blomenkamp K, Gautam M, et al. PiZ mouse liver accumulates polyubiquitin conjugates that associate with catalytically active 26S proteasomes. *PLoS One.* 2014;9(9):e106371.
31. Alam S, Li Z, Janciauskiene S, Mahadeva R. Oxidation of Z $\alpha 1$ -antitrypsin by cigarette smoke induces polymerization: a novel mechanism of early-onset emphysema. *Am J Respir Cell Mol Biol.* 2011;45(2):261–269.
32. Wilson AA, Murphy GJ, Hamakawa H, et al. Amelioration of emphysema in mice through lentiviral transduction of long-lived pulmonary alveolar macrophages. *J Clin Invest.* 2010;120(1):379–389.
33. Stoller JK, Aboussouan LS. A review of $\alpha 1$ -antitrypsin deficiency. *Am J Respir Crit Care Med.* 2012;185(3):246–259.
34. Hidvegi T, Schmidt BZ, Hale P, Perlmutter DH. Accumulation of mutant $\alpha 1$ -antitrypsin Z in the endoplasmic reticulum activates caspases-4 and -12, NF κ B, and BAP31 but not the unfolded protein response. *J Biol Chem.* 2005;280(47):39002–39015.
35. Lomas DA, Evans DL, Finch JT, Carrell RW. The mechanism of Z $\alpha 1$ -antitrypsin accumulation in the liver. *Nature.* 1992;357(6379):605–607.
36. Kamimoto T, Shoji S, Hidvegi T, et al. Intracellular inclusions containing mutant $\alpha 1$ -antitrypsin Z are propagated in the absence of autophagic activity. *J Biol Chem.* 2006;281(7):4467–4476.
37. Perlmutter DH. Alpha-1-antitrypsin deficiency: importance of proteasomal and autophagic degradative pathways in disposal of liver disease-associated protein aggregates. *Ann Rev Med.* 2011;62(1):333–345.
38. Faull SV, Elliston ELK, Gooptu B, et al. The structural basis for Z $\alpha 1$ -antitrypsin polymerization in the liver. *Sci Adv.* 2020;6(43):eabc1370.
39. Ordóñez A, Snapp EL, Tan L, et al. Endoplasmic reticulum polymers impair luminal protein mobility and sensitize to cellular stress in $\alpha 1$ -antitrypsin deficiency. *Hepatology.* 2013;57(5):2049–2060.
40. Tan L, Dickens JA, DeMeo DL, et al. Circulating polymers of A1-AT are present in all individuals with PiZZ A1-AT deficiency and are associated with COPD. *Eur Respir J.* 2014;43:1501–1504.
41. Lomas DA. An ECLIPSE view of alpha-1 antitrypsin deficiency. *Ann Am Thorac Soc.* 2016;13(Suppl 4):S326–S331.
42. Haq I, Irving JA, Saleh AD, et al. Deficiency mutations of $\alpha 1$ -antitrypsin differentially affect folding, function and polymerization. *Am J Respir Cell Mol Biol.* 2015;150:619071832005.
43. van't Wout EFA, Dickens JA, van Schadewijk A, et al. Increased ERK signalling promotes inflammatory signalling in primary airway epithelial cells expressing Z $\alpha 1$ -antitrypsin. *Hum Mol Genet.* 2014;23(4):929–941.
44. Gao W, Zhao J, Kim H, et al. $\alpha 1$ -Antitrypsin inhibits ischemia reperfusion-induced lung injury by reducing inflammatory response and cell death. *J Heart Lung Transplant.* 2014;33(3):309–315.
45. Jonigk D, Al-Omari M, Maegel L, et al. Anti-inflammatory and immunomodulatory properties of $\alpha 1$ -antitrypsin without inhibition of elastase. *Proc Natl Acad Sci U S A.* 2013;110(37):15007–15012.

46. Janciauskiene SM, Nita IM, Stevens T. α_1 -Antitrypsin, old dog, new tricks. α_1 -antitrypsin exerts in vitro anti-inflammatory activity in human monocytes by elevating cAMP. *J Biol Chem.* 2007;282(12):8573–8582.
47. Baraldo S, Turato G, Lunardi F, et al. Immune activation in α_1 -antitrypsin-deficiency emphysema. Beyond the protease–antiprotease paradigm. *Am J Respir Crit Care Med.* 2015;191(4):402–409.
48. Bergin DA, Reeves EP, Hurley K, et al. The circulating proteinase inhibitor α_1 antitrypsin regulates neutrophil degranulation and autoimmunity. *Sci Transl Med.* 2014;6(217):1–14.
49. He S-H, Xie H, Zhang X-J, Wang X-J. Inhibition of histamine release from human mast cells by natural chymase inhibitors. *Acta Pharmacol Sin.* 2004;25(6):822–826.
50. Churg A, Wang X, Wang RD, et al. Alpha1-antitrypsin suppresses TNF-alpha and MMP-12 production by cigarette smoke-stimulated macrophages. *Am J Respir Cell Mol Biol.* 2007;37(2):144–151.
51. Lu Y, Tang M, Wasserfall C, et al. Alpha1-antitrypsin gene therapy modulates cellular immunity and efficiently prevents type 1 diabetes in nonobese diabetic mice. *Hum Gene Ther.* 2006;17(6):625–634.
52. Churg A, Wang RD, Xie C, Wright JL. α_1 -Antitrypsin ameliorates cigarette smoke-induced emphysema in the mouse. *Am J Respir Crit Care Med.* 2003;168(2):199–207.
53. Xie C, Zay K, Wright JL, Churg A. Acute cigarette smoke-induced connective tissue breakdown is mediated by neutrophils and prevented by α_1 -antitrypsin. *Am J Respir Cell Mol Biol.* 2000;22:244–252.
54. Daemen MA, Heemskerk VH, van't Veer C, et al. Functional protection by acute phase proteins alpha(1)-acid glycoprotein and alpha(1)-antitrypsin against ischemia/reperfusion injury by preventing apoptosis and inflammation. *Circulation.* 2000;102(12):1420–1426.
55. Ikebe N, Akaike T, Miyamoto Y, et al. Protective effect of S-nitrosylated alpha(1)-protease inhibitor on hepatic ischemia-reperfusion injury. *J Pharmacol Exp Ther.* 2000;295(3):904–911.
56. Toldo S, Seropian IM, Mezzaroma E, et al. Alpha-1 antitrypsin inhibits caspase-1 and protects from acute myocardial ischemia-reperfusion injury. *J Mol Cell Cardiol.* 2011;51(2):244–251.
57. Petracche I, Fijalkowska I, Medler TR, et al. α_1 -antitrypsin inhibits caspase-3 activity, preventing lung endothelial cell apoptosis. *Am J Pathol.* 2006;169(4):1155–1166.
58. Lockett AD, Demark MV, Gu Y, et al. Effect of cigarette smoke exposure and structural modifications on the α_1 -antitrypsin interaction with caspases. *Mol Med.* 2012;18(3):445–454.
59. Quadri SM, Segall L, Perrot MD, Han B. Caspase inhibition improves ischemia-reperfusion injury after lung transplantation. *Am J Transplant.* 2005;5:292–299.
60. Mahadeva R, Atkinson C, Li Z, et al. Polymers of Z alpha1-antitrypsin co-localize with neutrophils in emphysematous alveoli and are chemotactic in vivo. *Am J Pathol.* 2005;166(2):377–386.
61. Mulgrew AT. Z 1-Antitrypsin polymerizes in the lung and acts as a neutrophil chemoattractant. *Chest.* 2004;125(5):1952–1957.
62. Marciniaik SJ, Ordóñez A, Dickens JA, et al. New concepts in alpha-1 antitrypsin deficiency disease mechanisms. *Ann Am Thorac Soc.* 2016;13(Suppl 4):S289–S296.
63. Pini L, Tiberio L, Venkatesan N, et al. The role of bronchial epithelial cells in the pathogenesis of COPD in Z-alpha-1 antitrypsin deficiency. *Respir Res.* 2014;15(1):1–10.
64. Hidvegi T, Stoltz DB, Alcorn JF, et al. Enhancing Autophagy with drugs or lung-directed gene therapy reverses the pathological effects of respiratory epithelial cell proteinopathy. *J Biol Chem.* 2015;290(50):29742–29757.
65. Fregonese L, Stolk J, Frants RR, Veldhuisen B. Alpha-1 antitrypsin null mutations and severity of emphysema. *Respir Med.* 2008;102(6):876–884.
66. Hood JM, Koep LJ, Peters RL, et al. Liver transplantation for advanced liver disease with alpha-1-antitrypsin deficiency. *N Engl J Med.* 1980;302(5):272–275.
67. Perlino E, Cortese R, Ciliberto G. The human alpha 1-antitrypsin gene is transcribed from two different promoters in macrophages and hepatocytes. *EMBO J.* 1987;6(9):2767–2771.
68. Hu C, Perlmuter DH. Cell-specific involvement of HNF-1beta in alpha(1)-antitrypsin gene expression in human respiratory epithelial cells. *Am J Physiol Lung Cell Mol Physiol.* 2002;282(4):L757–L765.
69. Li Y, Zhou L, Twining SS, Sugar J, Yue BY. Involvement of Sp1 elements in the promoter activity of the alpha1-proteinase inhibitor gene. *J Biol Chem.* 1998;273(16):9959–9965.
70. Molmenti E, Perlmuter DH, Rubin DC. Cell-specific expression of alpha 1-antitrypsin in human intestinal epithelium. *J Clin Invest.* 1993;92:2022–2034.
71. Morgan K, Marsters P, Morley S, et al. Oncostatin M induced alpha1-antitrypsin (AAT) gene expression in Hep G2 cells is mediated by a 3' enhancer. *Biochem J.* 2002;365(Pt 2):555–560.
72. Perlmuter DH, Cole FS, Kilbridge P, et al. Expression of the alpha 1-proteinase inhibitor gene in human monocytes and macrophages. *Proc Natl Acad Sci U S A.* 1985;82(3):795–799.
73. Frenzel E, Wrenger S, Immenschuh S, et al. Acute-phase protein 1-antitrypsin—a novel regulator of angiopoietin-like protein 4 transcription and secretion. *J Immunol.* 2014;192(11):5354–5362.
74. O'Brien ME, McCarthy C, Henry M, et al. Alpha-1 antitrypsin binds complement C3: a novel immune regulatory role. *Ir J Med Sci.* 2013;182:S440.
75. Carroll TP, Greene CM, O'Connor CA, et al. Evidence for unfolded protein response activation in monocytes from individuals with alpha-1 antitrypsin deficiency. *J Immunol.* 2010;184(8):4538–4546.
76. Winkler IG, Hendy J, Coughlin P, et al. Serine protease inhibitors serpin1 and serpina3 are down-regulated in bone marrow during hematopoietic progenitor mobilization. *J Exp Med.* 2005;201(7):1077–1088.
77. Borel F, Sun H, Zieger M, et al. Editing out five Serpinal paralogs to create a mouse model of genetic emphysema. *Proc Natl Acad Sci U S A.* 2018;115(11):2788–2793.
78. McElcaney NG, Stoller JK, Buist AS, et al. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute registry of α_1 -antitrypsin deficiency. *Chest.* 1997;111(2):394–403.
79. Stoller JK, Sandhaus RA, Turino G, et al. Delay in diagnosis of α_1 -antitrypsin deficiency: a continuing problem. *Chest.* 2005;128(4):1989–1994.
80. Campos MA, Wanner A, Zhang G, Sandhaus RA. Trends in the diagnosis of symptomatic patients with α_1 -antitrypsin deficiency between 1968 and 2003. *Chest.* 2005;128(3):1179–1186.

81. Stoller JK, Aboussouan LS, Kanner RE, et al. Characteristics of alpha-1 antitrypsin-deficient individuals in the long-term oxygen treatment trial and comparison with other subjects with chronic obstructive pulmonary disease. *Ann Am Thorac Soc.* 2015;12(12):1796–1804.
82. Gishen P, Saunders AJS, Tobin MJ, Hutchison DCS. Alpha-1-antitrypsin deficiency: the radiological features of pulmonary emphysema in subjects of Pi type Z and Pi type SZ: a survey by the British thoracic association. *Clin Radiol.* 1982;33(4):371–377.
83. Brantly ML, Paul LD, Miller BH, et al. Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms. *Am Rev Respir Dis.* 1988;138(2):327–336.
84. Parr DG, Stoel BC, Stolk J, Stockley RA. Pattern of emphysema distribution in α 1-antitrypsin deficiency influences lung function impairment. *Am J Respir Crit Care Med.* 2004;170(11):1172–1178.
85. Tobin MJ, Cook PJL, Hutchison DCS. Alpha 1 antitrypsin deficiency: the clinical and physiological features of pulmonary emphysema in subjects homozygous for Pi type Z A survey by the British Thoracic Association. *Brit J Dis Chest.* 1983;77(1):14–27.
86. Parr DG, Guest PG, Reynolds JH, et al. Prevalence and impact of bronchiectasis in α 1-antitrypsin deficiency. *Am J Respir Crit Care Med.* 2007;176(12):1215–1221.
87. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. *Am J Respir Crit Care Med.* 1998;158(1):49–59.
88. Piitulainen E, Eriksson S. Decline in FEV1 related to smoking status in individuals with severe α 1-antitrypsin deficiency (PiZZ). *Eur Respir J.* 1999;13(2):247–251.
89. Seersholt N, Kok-Jensen A, Dirksen A. Decline in FEV1 among patients with severe hereditary alpha 1-antitrypsin deficiency type PiZ. *Am J Respir Crit Care Med.* 1995;152(6):1922–1925.
90. Banauch GI, Brantly M, Izbicki G, et al. Accelerated spirometric decline in New York City firefighters with α 1-antitrypsin deficiency. *Chest.* 2010;138(5):1116–1124.
91. Wood AM, Harrison RM, Semple S, et al. Outdoor air pollution is associated with rapid decline of lung function in α -1-antitrypsin deficiency. *Occup Environ Med.* 2010;67(8):556.
92. Smith KC, Su WPD, Pittelkow MR, Winkelmann RK. Clinical and pathologic correlations in 96 patients with panniculitis, including 15 patients with deficient levels of α 1-antitrypsin. *J Am Acad Dermatol.* 1989;21(6):1192–1196.
93. Esnault VLM, Testa A, Audrain M, et al. Alpha1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. *Kidney Int.* 1993;43(6):1329–1332.
94. Davis ID, Burke B, Freese D, et al. The pathologic spectrum of the nephropathy associated with α 1-antitrypsin deficiency. *Hum Pathol.* 1992;23(1):57–62.
95. Greulich T, Nell C, Hohmann D, et al. The prevalence of diagnosed α 1-antitrypsin deficiency and its comorbidities: results from a large population-based database. *Eur Respir J.* 2017;49(1):1600154.
96. Tanash HA, Nilsson PM, Nilsson J-A, Piitulainen E. Clinical course and prognosis of never-smokers with severe alpha-1-antitrypsin deficiency (PiZZ). *Thorax.* 2008;63(12):1091–1095.
97. Stoller JK, Tomashefski J, Crystal RG, et al. Mortality in individuals with severe deficiency of α 1-antitrypsin findings from the National Heart, Lung, and Blood Institute registry. *Chest.* 2005;127(4):1196–1204.
98. Larsson C. Natural history and life expectancy in severe alpha-1-antitrypsin deficiency, Pi Z. *Acta Med Scand.* 1978;204(1–6):345–351.
99. Seersholt N, Kok-Jensen A, Dirksen A. Survival of patients with severe alpha 1-antitrypsin deficiency with special reference to non-index cases. *Thorax.* 1994;49(7):695.
100. Seersholt N, Dirksen A, Kok-Jensen A. Airways obstruction and two year survival in patients with severe alpha 1-antitrypsin deficiency. *Eur Respir J.* 1994;7(11):1985–1987.
101. Tomashefski JF Jr, Crystal RG, Wiedemann HP, et al. The bronchopulmonary pathology of alpha-1 antitrypsin (AAT) deficiency: findings of the death review committee of the national registry for individuals with severe deficiency of alpha-1 antitrypsin. *Hum Pathol.* 2004;35(12):1452–1461.
102. Franciosi AN, Hobbs BD, McElvaney OJ, et al. Clarifying the risk of lung disease in SZ α 1-antitrypsin deficiency. *Am J Respir Crit Care Med.* 2020;202(1):73–82.
103. Molloy K, McElvaney NG. Clarification of the risk of COPD in alpha-1 antitrypsin deficiency PiMZ heterozygotes. *Am J Respir Crit Care Med.* 2014;1–39.
104. Ortega VE, Li X, O'Neal WK, et al. The Effects of rare SERPINA1 variants on lung function and emphysema in SPIROMICS. *Am J Respir Crit Care Med.* 2020;201(5):540–554.
105. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis.* 2016;3(3):668–682.
106. Alpha 1-antitrypsin deficiency: memorandum from a WHO meeting. *Bull World Health Organ.* 1997;75(5):397–415.
107. Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. *Can Respir J.* 2012;19(2):109–116.
108. Ferrarotti I, Thun GA, Zorzetto M, et al. Serum levels and genotype distribution of α 1-antitrypsin in the general population. *Thorax.* 2012;67(8):669.
109. Perlmuter DH, May LT, Sehgal PB. Interferon beta 2/interleukin 6 modulates synthesis of alpha 1-antitrypsin in human mononuclear phagocytes and in human hepatoma cells. *J Clin Invest.* 1989;84(1):138–144.
110. Crystal RG. Alpha 1-antitrypsin deficiency, emphysema, and liver disease. Genetic basis and strategies for therapy. *J Clin Invest.* 1990;85(5):1343–1352.
111. Miravitles M, Herr C, Ferrarotti I, et al. Laboratory testing of individuals with severe 1-antitrypsin deficiency in three European centres. *Eur Respir J.* 2010;35(5):960–968.
112. Stoller JK. Detecting alpha-1 antitrypsin deficiency. *Ann Am Thorac Soc.* 2016;13(Suppl 4):S317–S325.
113. Crystal RG. Augmentation treatment for α 1 antitrypsin deficiency. *Lancet.* 2015;386(9991):318–320.
114. Laurell C-B, Eriksson S. The serum alpha-L-antitrypsin in families with hypo-alpha-L-antitrypsinemia. *Clin Chim Acta.* 1965;11:395–398.
115. Chapman KR, Burdon JGW, Piitulainen E, et al. Intravenous augmentation treatment and lung density in severe α 1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;386(9991):360–368.
116. Miravitles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of

- pulmonary disease in α_1 -antitrypsin deficiency. *Eur Respir J.* 2017;50(5):1700610.
117. Campos MA, Geraghty P, Holt G, et al. The biological effects of double-dose alpha-1 antitrypsin augmentation therapy: a pilot study. *Am J Respir Crit Care Med.* 2019;1200(3):318–326.
118. Rahaghi FF, Monk R, Ramakrishnan V, et al. Alpha-1 antitrypsin augmentation therapy improves survival in severely deficient patients with predicted FEV₁ between 10% and 60%: a retrospective analysis of the NHLBI Alpha-1 Antitrypsin Deficiency registry. *Int J Chron Obstruct Pulmon Dis.* 2020; 15:3193–3199.
119. Mohanka M, Khemasuwan D, Stoller JK. A review of augmentation therapy for alpha-1 antitrypsin deficiency. *Expert Opin Biol Ther.* 2012;12(6):685–700.
120. Dirksen A, Piitulainen E, Parr DG, et al. Exploring the role of CT densitometry: a randomised study of augmentation therapy in alpha1-antitrypsin deficiency. *Eur Respir J.* 2009;33(6):1345–1353.
121. Dirksen A, Dijkman JH, Madsen F, et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med.* 1999;160(5 Pt 1):1468–1472.
122. Wencker M, Banik N, Buhl R, et al. Long-term treatment of alpha1-antitrypsin deficiency-related pulmonary emphysema with human alpha1-antitrypsin. Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL)-alpha1-AT-study group. *Eur Respir J.* 1998;11(2):428–433.
123. Seersholtz N, Wencker M, Banik N, et al. Does α_1 -antitrypsin augmentation therapy slow the annual decline in FEV₁ in patients with severe hereditary α_1 -antitrypsin deficiency? *Eur Respir J.* 1997;10(10):2260–2263.
124. Hubbard RC, Crystal RG. Alpha-1-antitrypsin augmentation therapy for alpha-1-antitrypsin deficiency. *Am J Med.* 1988;84(6):52–62.
125. Hubbard RC, Sellers S, Czerski D, et al. Biochemical efficacy and safety of monthly augmentation therapy for alpha 1-antitrypsin deficiency. *JAMA.* 1988;260(9):1259–1264.
126. Hewers MD, Casolaro MA, Sellers SE, et al. Replacement therapy for alpha 1-antitrypsin deficiency associated with emphysema. *N Engl J Med.* 1987;316(17):1055–1062.
127. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2020 Report). *Am J Respir Crit Care Med.* 2019;1–141.
128. Chapman KR, Stockley RA, Dawkins C, et al. Augmentation therapy for α_1 antitrypsin deficiency: a meta-analysis. *COPD.* 2009;6(3):177–184.
129. McElvaney NG, Burdon J, Holmes M, et al. Long-term efficacy and safety of α_1 proteinase inhibitor treatment for emphysema caused by severe α_1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE). *Lancet Respir Med.* 2017;5(1):51–60.
130. Wencker M, Fuhrmann B, Konietzko N, et al. Longitudinal follow-up of patients with α_1 -protease inhibitor deficiency before and during therapy with IV α_1 -protease inhibitor. *Chest.* 2001;119(3):737–744.
131. Lieberman J. Augmentation therapy reduces frequency of lung infections in antitrypsin deficiency: a new hypothesis with supporting data. *Chest.* 2000;118(5):1480–1485.
132. Smith DJ, Ellis PR, Turner AM. Exacerbations of lung disease in alpha-1 antitrypsin deficiency. *Chronic Obstr Pulm Dis.* 2020;8(1):1–45.
133. Gulack BC, Mulvihill MS, Ganapathi AM, et al. Survival after lung transplantation in recipients with alpha-1-antitrypsin deficiency compared to other forms of chronic obstructive pulmonary disease: a national cohort study. *Transpl Int.* 2017;1–26.
134. Banga A, Gildea T, Rajeswaran J, et al. The natural history of lung function following lung transplantation for alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med.* 2014;190(3):274–281.
135. Caughey GH. Should alpha 1-antitrypsin-deficient patients with emphysema continue to receive alpha 1-antitrypsin after lung transplantation? *J Heart Lung Transplant.* 1993;12(4):708–709.
136. Teschler H. Long-term experience in the treatment of α_1 -antitrypsin deficiency: 25 years of augmentation therapy. *Eur Respir Rev.* 2015;24(135):46–51.
137. Yusa K, Rashid ST, Strick-Marchand H, et al. Targeted gene correction of α_1 -antitrypsin deficiency in induced pluripotent stem cells. *Nature.* 2011;478(7369):391–394.
138. Lomas DA, Hurst JR, Goopurtu B. Update on alpha-1 antitrypsin deficiency: new therapies. *J Hepatol.* 2016;65(2):413–424.
139. Brand P, Schulte M, Wencker M, et al. Lung deposition of inhaled 1-proteinase inhibitor in cystic fibrosis and 1-antitrypsin deficiency. *Eur Respir J.* 2009;34(2):354–360.
140. Vogelmeier C, Kirlath I, Warrington S, et al. The intrapulmonary half-life and safety of aerosolized alpha1-protease inhibitor in normal volunteers. *Am J Respir Crit Care Med.* 1997;155(2):536–541.
141. Siekmeier R. Lung deposition of inhaled alpha-1-proteinase inhibitor (Alpha1-PI)—problems and experience of alpha1-PI inhalation therapy in patients with hereditary alpha1-PI deficiency and cystic fibrosis. *Eur J Med Res.* 2010;15(Suppl 2):164.
142. Stolk J, Tov N, Chapman KR, et al. Efficacy and safety of inhaled α_1 -antitrypsin in patients with severe α_1 -antitrypsin deficiency and frequent exacerbations of COPD. *Eur Respir J.* 2019;54(5):1900673.
143. Mueller C, Flotte TR. Gene-based therapy for alpha-1 antitrypsin deficiency. *COPD.* 2013;10(Suppl 1):44–49.
144. Flotte TR. Adeno-associated virus-based gene therapy for inherited disorders. *Pediatr Res.* 2005;58(6):1143–1147.
145. Mueller C, Tang Q, Gruntman A, et al. Sustained miRNA-mediated knockdown of mutant AAT with simultaneous augmentation of wild-type AAT has minimal effect on global liver miRNA profiles. *Mol Ther.* 2009;1–11.
146. Lu Y, Choi Y-K, Campbell-Thompson M, et al. Therapeutic level of functional human alpha 1 antitrypsin (hAAT) secreted from murine muscle transduced by adeno-associated virus (rAAV1) vector. *J Gene Med.* 2006;8(6):730–735.
147. Song S, Morgan M, Ellis T, et al. Sustained secretion of human alpha-1-antitrypsin from murine muscle transduced with adeno-associated virus vectors. *Proc National Acad Sci U S A.* 1998;95(24):14384–14388.
148. Song S, Embury J, Laipis P, et al. Stable therapeutic serum levels of human alpha-1 antitrypsin (AAT) after portal vein injection of recombinant adeno-associated virus (rAAV) vectors. *Gene Ther.* 2001;8(17):1299–1306.
149. Brantly ML, Chulay JD, Wang L, et al. Sustained transgene expression despite T lymphocyte responses in a clinical trial of rAAV1-AAT gene therapy. *Proc National Acad Sci U S A.* 2009;106(38):16363–16368.

150. Gernoux G, Gruntman AM, Blackwood M, et al. Muscle-directed delivery of an AAV1 vector leads to capsid-specific T cell exhaustion in nonhuman primates and humans. *Mol Ther.* 2020;28(3):747–757.
151. Wooddell CI, Blomenkamp K, Peterson RM, et al. Development of an RNAi therapeutic for alpha-1-antitrypsin liver disease. *JCI Insight.* 2020;5(12):e135348.
152. Rashid ST, Corbneau S, Hannan N, et al. Modeling inherited metabolic disorders of the liver using human induced pluripotent stem cells. *J Clin Invest.* 2010;120(9):3127–3136.
153. Somers A, Jean J-C, Sommer CA, et al. Generation of transgene-free lung disease-specific human induced pluripotent stem cells using a single excisable lentiviral stem cell cassette. *Stem Cells.* 2010;28(10):1728–1740.
154. Wilson AA, Ying L, Liesa M, et al. Emergence of a stage-dependent human liver disease signature with directed differentiation of alpha-1 antitrypsin-deficient iPS cells. *Stem Cell Rep.* 2015;4(5):873–885.
155. Kaserman JE, Hurley K, Dodge M, et al. A highly phenotyped open access repository of alpha-1 antitrypsin deficiency pluripotent stem cells. *Stem Cell Rep.* 2020;15(1):242–255.
156. Song C-Q, Wang D, Jiang T, et al. In vivo genome editing partially restores alpha1-antitrypsin in a murine model of AAT deficiency. *Hum Gene Ther.* 2018;29(8):853–860.

CHAPTER 40

Course and Treatment of Chronic Obstructive Pulmonary Disease

M. Bradley Drummond

Robert A. Wise

INTRODUCTION

In past decades, the treatment of chronic obstructive pulmonary disease (COPD) has been approached by many physicians and patients alike with a nihilistic attitude, assuming that the disease was progressive, incurable, and untreatable. More recently, as our understanding of the clinical epidemiology and value of therapy of COPD has improved, this attitude has changed. Physicians have come to approach COPD in the same way as other chronic diseases with goals of improving quality of life, functional capacity, and prolonged survival. With a comprehensive approach to treatment, COPD is compatible with prolonged survival, good quality of life, and independent functional status for many who have this illness. The purpose of this chapter is to summarize the current understanding of the course of COPD and best approaches to treatment.

OVERVIEW OF COPD

COPD is a disorder that is characterized by slow emptying of the lung during a forced expiration. In practice, this is measured as the forced expiratory volume in 1 second/forced vital capacity (FEV₁/FVC) ratio, and the arbitrary definition of airflow obstruction is generally taken to be an FEV₁/FVC ratio lower than 0.70.¹ Because the rate of emptying of the lung falls with advancing age, many elderly individuals demonstrate airflow obstruction even in the absence of a clinical diagnosis of COPD. For this reason, an alternative criterion to define airflow obstruction incorporates lower limit of normal thresholds instead of the fixed ratio criteria.² Several disorders cause chronic airflow obstruction—long-standing asthma, cystic fibrosis, bronchiectasis, bronchiolitis obliterans, lymphangiomyomatosis, panbronchiolitis, silicosis, Sjögren syndrome, and diffuse interstitial processes such as eosinophilic granuloma and sarcoidosis. The diagnosis of COPD is usually limited to individuals who have chronic airflow obstruction associated with tobacco smoke or some other noxious inhalant, and it is usually not difficult to distinguish it from other causes of chronic airflow obstruction. The most common disorders associated with COPD are emphysema and chronic bronchitis. *Emphysema* is defined anatomically by air-space enlargement due to disappearance of alveolar septae (Chapter 37). This leads to the characteristic loss of elastic recoil, which, in turn, causes slowing of airflow from the lungs, hyperinflation, and air trapping. *Chronic bronchitis* is characterized by chronic cough and sputum production, which is present in about one out of three people with early COPD. Chronic cough and sputum production in cigarette smokers is often, but not always, associated with chronic airflow obstruction. When chronic mucus hypersecretion is associated with airflow obstruction, it is often called *chronic obstructive bronchitis*. Although people with nonobstructive mucus hypersecretion (nonobstructive chronic bronchitis) have a greater risk for acute respiratory illness, most such individuals will not progress

to airflow limitation, and therefore, the term “pre-COPD” should be avoided.³ It is unknown whether maintenance treatment of nonobstructive chronic bronchitis is beneficial. The anatomic correlates of chronic bronchitis are mucus gland hyperplasia and goblet cell metaplasia in large- and medium-sized airways.⁴ Patients with COPD also have small- and medium-sized airway involvement with inflammation, narrowing, tortuosity, mucus plugging, and fibrosis that contributes to the airflow limitation. As the disease evolves, there is obliteration of small airways. Some patients with a long-standing history of asthma develop airflow obstruction that is not completely reversible, episodes of cough and wheeze, and chronic sputum production. These individuals are often classified as having *chronic asthmatic bronchitis* and have a better prognosis for survival than those with tobacco-related COPD.

NATURAL HISTORY OF COPD

COPD occurs in middle age and later because of the age-related decline in lung function over time. Typically, peak lung function occurs during the third or fourth decades of life. Healthy nonsmoking adults lose FEV₁ at a rate of 30 mL/year, thought to be the consequence of the aging-related loss of elastic recoil of the lung. Persons who develop COPD may start in early adulthood with low levels of lung function or with a normal rate of decline or may have normal young adult lung function and have increased rates of decline.^{5,6} Studies of patients with COPD show an average annual decline in FEV₁ of 45 to 69 mL/year (Fig. 40-1A). However, there may be considerable heterogeneity between patients and over time.^{7,8} This leads to the insidious loss of ventilatory reserve capacity that often is asymptomatic and unrecognized by patients and physicians alike. Chronic bronchitis may be dismissed as an innocent “smoker’s cough” because patients fail to understand that it is abnormal to produce daily sputum. As ventilatory reserve decreases, people with mild COPD tend to limit strenuous activities, so breathlessness with activities of daily living is not ordinarily an early symptom of the disease. When the ventilatory reserve decreases to the extent that mild exertion such as climbing stairs, bed making, or carrying groceries is limited, patients tend to seek medical advice. In some cases, the first clinical presentation of disease is an acute episode of bronchospasm, dyspnea, or even respiratory failure in association with a respiratory infection or exposure to respiratory irritants. Thus, the onset of COPD may appear precipitous even though it is the cumulative result of decades of progression.

People who discontinue smoking with mild to moderate degrees of airflow obstruction cease the rapid decline in FEV₁ and have better survival (Fig. 40-1B).^{9,10,11} The improvement in survival depends largely upon the stage of disease. Persons who quit smoking with earlier disease have better outcomes compared with those who continue to smoke or those who quit smoking later in the disease. Once the disease is advanced, the inflammatory response may persist, and the proportional loss of lung function tends to progress. Because there are many years of asymptomatic decline in lung function, it is possible to diagnose COPD with forced expiratory spirometry before the disease is apparent and implement aggressive smoking intervention programs. There is a consensus that smokers with respiratory symptoms should be tested for COPD with spirometry. However, there is debate whether it is of value to screen for COPD among all cigarette smokers.¹² Opponents of using spirometry for case-finding argue that the finding of a normal test would not alter physician behavior because all smokers should be encouraged to quit. It has also been argued that a normal spirometry test might provide a false sense of complacency for active smokers. Those who support the use of spirometry for COPD case-finding argue that early detection and aggressive smoking intervention have been

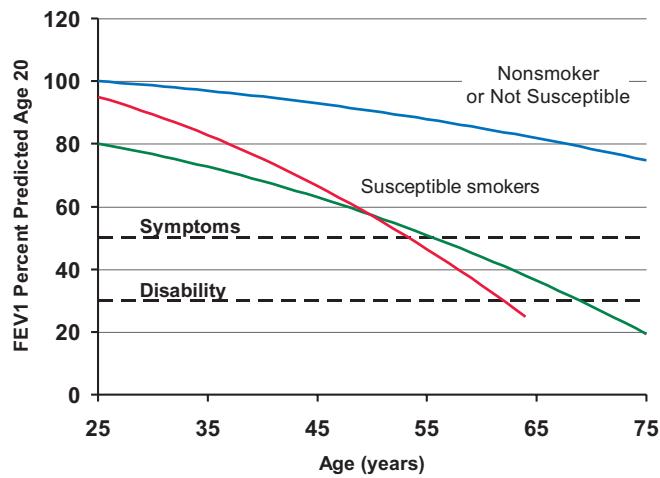
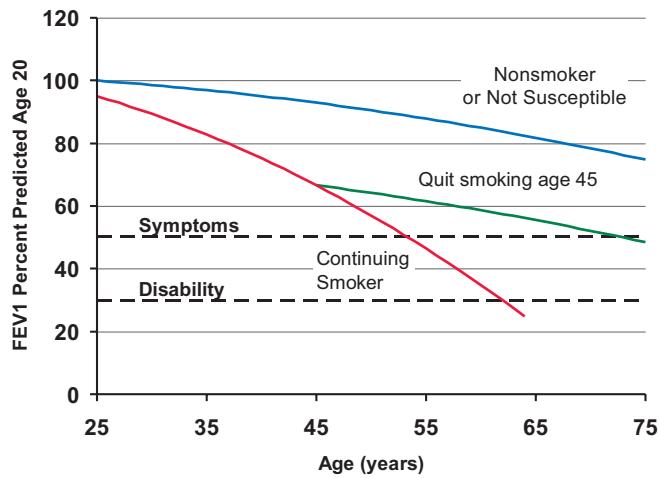
**A**

Figure 40-1 A. The natural history of COPD is presented for three hypothetical individuals. Pulmonary function is plotted as the percent of predicted lung function for a young adult who has attained maximal lung growth. Those who do not smoke or are not susceptible to cigarette smoke typically lose about 25% of their young adult lung function throughout life. Individuals are susceptible to the adverse effects of smoking because of increased decline of lung function, or low lung function in young adult life. Although the abnormality of lung function is detectable for many years, symptoms do not develop until there is loss of approximately 50% of lung function (*upper dashed line*), which occurs in middle age or later. If the disease progresses, it may lead to

**B**

substantial disability within a decade of the onset of symptoms (*lower dashed line*). **B.** The natural history of COPD is displayed for a hypothetical continuing smoker, and an individual who quit smoking at age 45. The axes are identical to those in (A). If an individual cease smoking in the asymptomatic phase of COPD, the rate of decline of lung function reverts toward normal. In this example, the detection of abnormal lung function and cessation of smoking has a substantial effect of delaying the onset of respiratory symptoms. This plot is modified from the work of Fletcher and Peto and is commonly referred to as Fletcher-Peto curves.

proven to halt disease progression and improve survival, and the finding of abnormal spirometry may encourage patients and health-care professionals to be more aggressive with smoking cessation. Moreover, some evidence points to the benefits of drug therapy in terms of lung function decline and survival in patients with mild to moderate airflow obstruction.^{13–15}

With the progression of COPD comes progressive exercise limitation.¹⁶ This is due to the increased work of breathing as ventilation increases with exercise. With increased respiratory rate, patients develop dynamic hyperinflation—a condition in which the end-expiratory lung volume does not return to the static end-expiratory volume of functional residual capacity (FRC). The hyperinflation that occurs causes increased work of breathing and exacerbates dyspnea. An indicator of dynamic hyperinflation is the inspiratory capacity (IC), which progressively falls with increasing ventilation. Measures that reduce dynamic hyperinflation, increasing IC, can improve exercise capacity. These include alterations in breathing pattern, oxygen supplementation, and use of inhaled bronchodilators. Similarly, episodes of anxiety can lead to tachypnea that induces dynamic hyperinflation and exacerbates the experience of dyspnea at rest. These episodes can often be minimized by explanation of the phenomenon to the patient and caregivers as well as judicious use of self-relaxation, pursed-lip breathing, and anxiolytics.

As COPD progresses, ventilation-perfusion inhomogeneity causes an increase in the alveolar–arterial oxygen difference. Eventually, alveolar hypoxemia leads to pulmonary hypertension, which manifests as cor pulmonale. The alveolar hypoxemia may be compounded by alveolar hypoventilation—manifested by arterial hypercapnia. Physical findings indicative of cor pulmonale are venous engorgement, edema, and physical findings of pulmonary hypertension and right ventricular failure including elevated venous pressure, accentuated pulmonic second heart sound, right ventricular heave, tricuspid regurgitation murmur, hepatosplenomegaly, and ascites. Chest imaging shows central enlargement of the pulmonary

arteries. Once cor pulmonale is clinically apparent, survival is markedly reduced in proportion to the impairment of functional capacity.

Patients with advanced COPD may restrict their activities to a bed-and-chair lifestyle because of severe exercise incapacitation. This limitation can lead to social isolation, depression, and skeletal muscle deconditioning, which, in turn, further restrict activity and impair quality of life. Protein and calorie malnutrition occur as the consequence of impaired nutritional intake caused by dyspnea.¹⁷ Malnutrition is augmented by increased metabolic demands caused by increased basal oxygen consumption, inefficient skeletal muscle oxygen utilization, and cachexia-producing cytokines such as tumor necrosis factor α (TNF- α).¹⁸

DIAGNOSIS OF COPD

Physical examination and chest imaging are insensitive methods for diagnosis of COPD. Physical findings of hyperinflated lungs such as low-lying diaphragm, decreased breath sounds, and hyperresonant chest percussion are highly specific for COPD, but usually only in advanced disease.^{19,20} One study has suggested that a distance between the thyroid cartilage and the sternal notch less than 4 cm in a smoker older than age 45 is highly indicative of the presence of COPD.²¹ Clubbing of the fingers is rare in COPD and, if present, suggests another diagnosis such as bronchiectasis, asbestosis, or lung cancer. High-resolution computed tomography (HRCT) of the lung is useful in establishing the presence of emphysema. Quantitative analysis of HRCT is a useful technique for early detection of emphysema but is not widely available in clinical practice at this time. α_1 -Antitrypsin deficiency is an uncommon, but not rare, condition associated with premature emphysema. **Table 40-1** lists conditions that suggest the presence of α_1 -antitrypsin deficiency. Some experts advise that all patients with emphysema or fixed airflow obstruction should be tested for α_1 -antitrypsin because treatments are available for those with the most severe form of deficiency.^{22,23} HIV/AIDS also is associated with premature emphysema and accelerated lung

TABLE 40-1 Conditions Suggesting α 1-Antitrypsin Deficiency

| |
|--|
| Early-onset emphysema (age under 45 years) |
| Emphysema in a nonsmoker |
| Emphysema predominantly in lung bases (panacinar) |
| Necrotizing panniculitis (Weber–Christian disease) |
| c-ANCA positive vasculitis (e.g., granulomatosis with polyangiitis) |
| Family history of early-onset emphysema or non-smoking-related emphysema |
| Family history of cirrhosis |
| Bronchiectasis without other etiology |

function decline, and screening for HIV should be performed for persons with emphysema and HIV risk factors such as intravenous drug use or high-risk sexual activity.^{24,25}

The diagnosis of COPD, classification of its severity, and progression of the disease can be monitored with spirometry, a simple, noninvasive, and inexpensive test. The FEV₁/FVC ratio, reflecting the rate of emptying of the lung, is used to define the presence of an obstructive ventilatory defect, commonly defined as a ratio less than 0.70 or below the lower limit of normal. Once airflow obstruction is established, the severity of the airflow limitation is classified by the reduction of FEV₁ compared with a healthy reference population. Lung volume measurements, by plethysmography, helium dilution, nitrogen washout, or single-breath methods typically show hyperinflation (elevated TLC) and air trapping (elevated residual volume [RV]), and thus are useful to exclude restrictive lung diseases. The carbon monoxide diffusing capacity (DL_{CO}) is an indicator of emphysema and is an independent predictor of mortality.

COPD is categorized based on the severity of airflow obstruction, presence of symptoms, propensity for exacerbations, and radiographic appearance. Airflow obstruction is based on spirometry (Table 40-2); symptoms are elicited with standard questionnaires such as the COPD Assessment Test (CAT)^{26,27} and mMRC dyspnea scale (Table 40-3); exacerbation risk is determined primarily by a history of previous exacerbations requiring treatment;²⁸ and emphysema is quantified by CT.^{29,30}

PROGNOSIS OF COPD

The prognosis in COPD may vary widely. Physicians are poor prognosticators of survival in COPD.²² In part, this is because the disease is one of widely varying rates of progression, and in part, this

TABLE 40-3 Modified Medical Research Council Dyspnea Scale (mMRC Scale)

| Grade | Description |
|-------|---|
| 0 | Not troubled with breathlessness except with strenuous exercise |
| 1 | Troubled by shortness of breath when hurrying on the level or walking up a slight hill |
| 2 | Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level |
| 3 | Stops for breath after walking about 100 yards or after a few minutes on the level |
| 4 | Too breathless to leave the house or breathless when dressing or undressing |

Data from Celli BR, MacNee W. ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–946.

is because death is often due to susceptibility to intercurrent illness and other smoking-related illness such as lung cancer rather than progressive respiratory failure. Recent studies have demonstrated heterogeneity in lung function decline, with some patients with COPD having little or no decline in FEV₁ over time.^{7,8}

Several factors have been identified that predict poor survival in COPD. These include low FEV₁, low inspiratory capacity, active smoking status, hypoxemia, poor nutrition, the presence of cor pulmonale, resting tachycardia, low exercise capacity, severe dyspnea, poor health-related quality of life, anemia, frequent or severe exacerbations, comorbid illnesses, and low DL_{CO}.^{31,32} Patients with moderate to very severe airflow limitation and a history of exacerbations have about 3% annual mortality if treated with bronchodilators alone. All-cause mortality is reduced by about 40% if inhaled corticosteroids are added to the treatment regimen.^{33,34} If a patient reports that they are unable to walk 100 m without stopping because of breathlessness, the 5-year survival is only 30%.³⁵ A multidimensional prognostic index that takes into account several indicators of COPD prognosis is the BODE index (body mass index [BMI], obstructive ventilatory defect severity, dyspnea severity, and exercise capacity).^{36,37} See Table 40-4 for calculation of the BODE prognostic score. The components are derived from measures of the BMI (weight in kg/height m²), FEV₁ percent predicted, and the modified Medical Research Council dyspnea score (Table 40-3). A BODE score greater than 7 is associated with a 30% 2-year mortality, whereas a score of 5 to 6 is associated with 15% 2-year mortality. If the BODE score is less than 5, the 2-year mortality is less than

TABLE 40-2 Classification of Severity of Airflow Limitation in COPD

| Ventilatory Impairment | Characteristics |
|----------------------------------|---|
| I Mild COPD ^a | FEV ₁ \geq 80% predicted |
| II Moderate COPD ^a | FEV ₁ 50%–79% predicted |
| III Severe COPD ^a | FEV ₁ 30%–49% predicted |
| IV Very severe COPD ^a | FEV ₁ <30% predicted or <50% predicted with room air Pa _{O₂} <60 mm Hg (8.0 kPa) |

^aPostbronchodilator FEV₁/FVC \leq 0.70.

Data from The 2021 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD).

TABLE 40-4 Calculation of the BODE Index^a

| Variable | Points on the BODE Index | | | |
|--------------------------------------|--------------------------|---------|-----------|------------|
| | 0 | 1 | 2 | 3 |
| FEV ₁ (% predicted) | \geq 65 | 50–64 | 36–49 | \leq 35 |
| Distance walked in 6 min (m) | \geq 350 | 250–349 | 150–249 | \leq 149 |
| mMRC dyspnea scale | 0–1 | 2 | 3 | 4 |
| Body mass index (kg/m ²) | >21 | | \leq 21 | |

^aThe BODE index is calculated as the sum of points from each row.

Reproduced with permission from Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–1012.

TABLE 40-5 Calculation of the ADO Index^a

| Variable | Points on the ADO Index | | | | | |
|--------------------------------|-------------------------|-------|-------|-------|-------|-----|
| | 0 | 1 | 2 | 3 | 4 | 5 |
| FEV ₁ (% predicted) | ≥65 | 36–64 | ≤35 | — | — | — |
| mMRC dyspnea scale | 0–1 | 2 | 3 | 4 | — | — |
| Age (years) | 40–49 | 50–59 | 60–69 | 70–79 | 80–89 | ≥90 |

^aThe ADO index is calculated as the sum of points from each row.

Adapted with permission from Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet.* 2009;374(9691):704–711.

10%. In settings where the 6-minute walk test is not available, the ADO index (age, dyspnea, and obstruction) also provides useful prognostic information (Table 40-5).³⁸ The ADO index ranges from 0 to 10 points, with each point increase in the index associated with a 42% marginal increase in odds of death at 3 years for patients with long-standing and severe COPD.

TREATMENT OF STABLE COPD

The goals of treatment of COPD are to prevent progression and complications of the disease, relieve symptoms, improve exercise capacity, improve quality of life, prevent and treat exacerbations, and improve survival.

■ Education

The diagnosis of COPD can be a life-changing event for people, so understanding the nature and prognosis of the disease is an important and underemphasized aspect of care. There is a wide divergence of understanding of the implications of having COPD, and many patients do not understand that COPD comprises both the diagnoses of emphysema and chronic bronchitis. Table 40-6 lists topics that should be discussed with COPD patients. It is neither possible nor effective to cover all these topics in a single session, so

TABLE 40-6 Patient Education Topics for Management of COPD

| |
|---|
| Risk factors for COPD |
| Smoking cessation advice and instruction |
| Reduction of noxious environmental exposures |
| Immunization for influenza and pneumococcus |
| Respiratory hygiene and avoidance of infections |
| Nature and prognosis of COPD |
| Indications, dose, benefits, and adverse effects of medications |
| Proper inhaler and nebulizer use |
| Strategies to improve adherence with prescribed treatment |
| Pacing, arm support, pursed lip breathing, and other strategies to minimize dyspnea |
| Importance of regular exercise and social interaction |
| Options for pulmonary rehabilitation programs |
| Recognition and early treatment of exacerbations |
| Indications for and proper use of supplemental oxygen |
| Options for surgical management if indicated |
| Advance directives for end-of-life care |

several sessions with repetition and expansion of the educational messages are necessary. Supplemental written materials or referral to a health educator also is necessary for many patients. Local and national volunteer health organizations provide useful educational materials and group educational sessions (e.g., www.copdfoundation.org, www.lung.org). Special counseling is needed for patients with α₁-antitrypsin deficiency and their family members to determine whether genetic testing is necessary or desired. In patients with advanced disease, discussions about end-of-life planning and advance directives regarding life support are often welcomed by patients and initiate discussions between the patient and family. Patients should be encouraged to discuss information that they obtain from newspapers or the Internet, as some may be instructive, but others are incorrect. Physicians should be prepared to deal with patients' sense of guilt, as many view COPD as a self-induced disease. Caregivers need to address the reality that COPD is often stigmatized by patients, their families, and other healthcare providers. The physician should let the patient understand that nicotine dependence is a strong physical addiction and difficulty quitting smoking is not a measure of moral weakness or lack of will. The general message provided should be realistic, but positive. Current treatments for COPD can improve quality of life, improve activity levels, maintain social interactions, and reduce the frequency of complications.

■ Prevention of COPD Progression and Complications

Presently, there are no proven treatments that prevent the progression of COPD in patients who continue to smoke cigarettes. *Smoking cessation*, however, does prevent the excessive decline in lung function and should be a primary goal for physicians caring for COPD patients. Patients with mild or moderate COPD may not know that they have underlying lung disease that can be halted by smoking cessation or may adopt a fatalistic attitude that it is too late for help. Even severely impaired patients who are dyspneic at rest or use continuous oxygen may continue to smoke cigarettes or relapse after quitting. A smoking history should be obtained at each patient encounter because many patients fail to volunteer the extent of their smoking or report a smoking relapse following cessation. In patients who do smoke, achieving cessation should be a primary and persistent goal of treatment.³⁹ Approaches to smoking cessation are given in detail in Chapter 41. For patients who do smoke, a direct, unambiguous, and personalized smoking cessation message should be given by the physician. The message should emphasize the harm of continued smoking, the benefits of cessation in terms of activities that are meaningful for the individual, and the understanding that smoking cessation is a realistic and achievable goal. Techniques of motivational interviewing are readily learned and are effective in changing health behaviors.⁴⁰ Assistance with pharmacologic adjuncts such as nicotine replacement therapy, varenicline, or bupropion and referral to smoking cessation groups should be offered. Follow-up of smoking status and repeated smoking cessation messages should be performed at each encounter.

Exposure to respiratory irritants should be avoided in the workplace as well as the home. Although heavy occupational dust exposure rarely is the primary cause of COPD, exposure to dusty occupational jobs in smokers can increase the lung function deterioration from smoking and increase symptoms of cough and sputum.⁴¹ In developing countries, heavy exposure to particulates from burning of biomass fuels is associated with COPD, even in the absence of cigarette smoking.^{42,43} Efforts to improve indoor air quality may be effective in reducing symptoms and disease progression. Respiratory protective equipment should be worn by patients with COPD exposed to heavy dust concentrations. There is no level of FEV₁ that absolutely prohibits the use of respiratory protective equipment, but patients with COPD often experience untoward breathlessness with

these masks because of the increased dead space and increased inspiratory resistance. Thus, many patients with COPD need to change their work environment if they cannot tolerate protective devices. If COPD is complicated by allergy or overlaps with allergic asthma, environmental control measures should be instituted to the extent that these strategies are helpful. Smoking of marijuana and cocaine may cause airway irritation, and although there is no convincing evidence that they contribute to progression of COPD, their use ought to be discouraged. Occasionally, heavy daily marijuana smokers will develop giant bullous emphysema, which has been called “marijuana lung,” but the causality remains to be established.^{44,45}

Pneumococcal vaccination is recommended and has been shown to reduce community-acquired pneumonia and possibly reduce exacerbation frequency in COPD.⁴⁶ Annual inactivated *influenza immunization* can prevent subsequent exacerbations due to influenza infections.⁴⁷ High-potency influenza immunization is recommended for older patients who may have an impaired immune response to the vaccine. During influenza epidemics, the use of neuraminidase inhibitors such as oseltamivir or RNA polymerase inhibitors such as baloxavir can minimize severity of infection if taken within 48 h of onset of illness and are useful against both influenza A and B and may limit the spread of infection. Peramivir, an injectable form of neuraminidase inhibitor, is now available for treatment of individuals with respiratory failure.

Replacement therapy with α_1 -antitrypsin should be considered for those individuals with severe deficiency. Observational studies suggest that individuals with moderate degrees of impairment (FEV₁ 35%–65% predicted) appear to benefit most in terms of preservation of lung function and improved survival.⁴⁸ Studies of HRCT progression of emphysema indicate a measurable benefit across a wider range of lung function.^{49,50} The human plasma-derived preparation of α_1 -antitrypsin is administered intravenously in a dose of 60 mg/kg weekly. Replacement treatment is derived from pooled human plasma, so immunization for hepatitis A and B is suggested. IgA deficiency may increase the risk of allergic reactions and therefore some authorities recommend testing for IgA levels before initiating therapy.

Screening for lung cancer with low-dose CT of the chest is recommended for individuals aged 50 to 80 years with a 20-pack-year smoking history who currently smoke or have quit within the last 15 years. Many individuals with COPD meet these criteria, and these individuals should undergo shared decision-making with their clinician. The discussions should include potential benefits and harms of screening.

■ Drug Therapy

Over the past several decades, the evidence base for use of drug therapy in COPD has expanded and provides an objective and generally optimistic picture that such treatment is effective. Bronchodilators and anti-inflammatory agents are used to reverse bronchoconstriction, improve lung function, improve quality of life, increase exercise capacity, and prevent exacerbations. Recent evidence however suggests that a combination of inhaled steroids and long-acting bronchodilators may improve survival as well as reduce exacerbations.^{33,34} There is a poor correlation between the effect of bronchodilating drugs on lung function and symptom relief, so monitoring of treatment requires attention to patient-reported outcomes as well as lung function. Small amounts of bronchodilation can cause considerable improvement in functional capacity through decrease in dynamic exercise hyperinflation, and reduction in days of exacerbation can lead to considerable improvement in patients' quality of life.⁵¹

Bronchodilators

The usual approach to drug treatment for COPD is to sequentially add agents using the minimum number of agents and the most

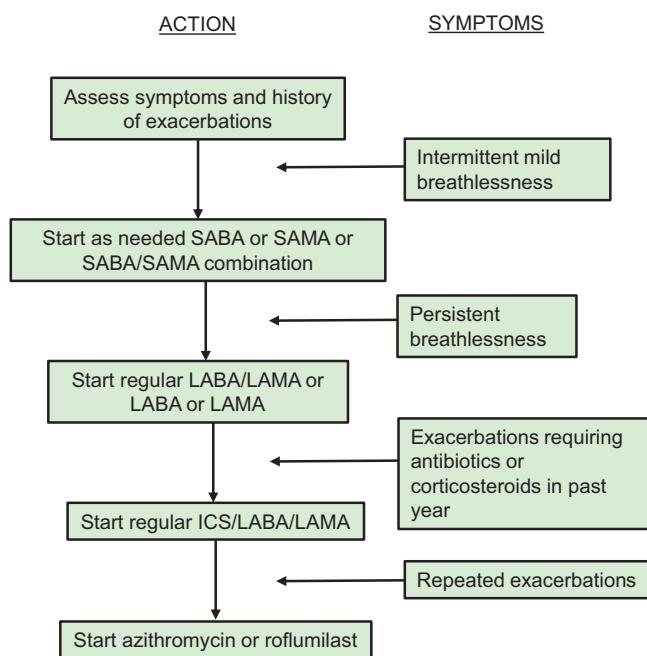


Figure 40-2 Flow chart for pharmacologic management for people with COPD. Treatment is based on step-up therapy depending on patient symptoms and frequency of exacerbations. Patients should be re-evaluated every 3 to 12 months for step-up or step-down of treatment. Evaluation for exacerbations should be contemporaneous with evaluation for symptoms, and ICS added to bronchodilators; however, ICS should usually not be given without bronchodilators. Patients with eosinophilia have a better response to ICS. ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist.

convenient dosing schedule, starting with the agents having the greatest benefit, best tolerance, and lowest cost. One approach to step-up therapy is provided in Fig. 40-2. Inhaled bronchodilators are the foundation of treatment for COPD. They are given on a regular basis to maintain bronchodilation and on an as needed basis for relief of symptoms.^{52,53} Most breathless patients benefit from regular use of a maintenance bronchodilator. Both β -agonist and anticholinergic classes are available in short-duration (4–6 h) and long-duration (12–24 h) forms (Table 40-7). The choice of bronchodilator class and duration of effect depends upon the preference of the patient, a suitable device, and the cost of the preparation. Combination of different classes of bronchodilators is often more effective than increasing the dose of a single agent, and combination inhalers with long-acting bronchodilators can simplify treatment regimens.⁵⁴ Patients with advanced COPD often use a combination of bronchodilators, including long-acting maintenance anticholinergics and β -agonists as well as symptomatic use of shorter-acting bronchodilators. Individuals with exacerbations, particularly those with eosinophilia, may benefit from a combination inhaler of corticosteroids and long-acting bronchodilator.^{55,56} Chronic use of systemic corticosteroids should be reserved for individuals with very frequent or life-threatening exacerbations in those cases where discontinuation of steroids cannot be tolerated. Response to treatment is judged by symptomatic improvement, functional status, frequency of exacerbations, and spirometry. If patients are doing well for 6 to 12 months on a stable treatment regimen, then it is reasonable to see if a trial withdrawal of one of the drug components can be tolerated.

Inhaled corticosteroids do not alter the progression of COPD in those who continue to smoke.^{57,58} Inhaled corticosteroids are most useful

TABLE 40-7 Inhaled Bronchodilators

| Drug Name | Dosage/Frequency | Formulation |
|---|---|--|
| β-Sympathomimetics | | |
| Olodaterol | | Soft mist inhaler, 5 µg |
| Albuterol | 2 inhalations q4–6h 3 mL nebulized q4–6h | Metered-dose inhaler, 90 µg/puff Nebulized solution 1.25–2.5 mg/3 mL |
| Levalbuterol | 2 inhalations q4–6h 3 mL nebulized TID | Metered-dose inhaler, 45 µg/puff Nebulized solution 0.63–1.25 mg/3 mL |
| Salmeterol | 1 inhalation BID | Dry powder inhaler, 50 µg/dose |
| Formoterol | 1 capsule inhaled BID 2 mL nebulized BID | Dry powder inhaler, 12 µg/capsule Nebulized solution 20 µg/2 mL |
| Arformoterol | 2 mL nebulized BID | Nebulized solution 15 µg/2 mL |
| Indacaterol | 1 capsule daily | Dry powder inhaler, 75 µg/capsule |
| Anticholinergic Bronchodilators | | |
| Ipratropium | 2 puffs q4–6h 2.5 mL nebulized q6–8h | Metered-dose inhaler, 17 µg/puff Nebulized solution 0.5 mg/2.5 mL |
| Tiotropium | 1 inhalation daily 2 inhalations daily | Dry powder inhaler 18 µg/dose Soft Mist inhaler 2.5 µg/inhalation |
| Aclidinium | 1 inhalation BID | Dry powder inhaler 400 µg/dose |
| Reverfenacin | 3 mL nebulized daily | Nebulized solution 175 µg/3 mL |
| Glycopyrrrolate | 1 inhalation BID 1 mL nebulized BID | Dry powder inhaler 15.6 µg/dose Nebulized solution 25 µg/mL |
| Umeclidinium | 1 inhalation daily | Dry powder inhaler 62.5 µg |
| Combination Bronchodilator Therapies | | |
| Ipratropium/albuterol | 1 puff q6h | Soft mist inhaler, 20 µg/100 µg/inhalation |
| Umeclidinium/vilanterol | 1 inhalation daily | Dry powder inhaler, 62.5 µg/25 µg/inhalation |
| Tiotropium/olodaterol | 2 inhalations daily | Soft mist inhaler 2.5 µg/2.5 µg/inhalation |
| Glycopyrrrolate/formoterol | 2 inhalations BID | Metered-dose-inhaler 18 µg/9.6 µg/inhalation |
| Glycopyrrrolate/indacaterol | 1 inhalation BID | Dry powder inhaler 15.6 µg/27.5 µg/inhalation |
| Aclidinium/formoterol | 1 inhalation BID | Dry powder inhaler 400 µg/12 µg/inhalation |

in patients who have features of asthma and in COPD patients who have frequent exacerbations. Eosinophilia is a biomarker that predicts a particularly good response to inhaled corticosteroids.⁵⁹ Inhaled corticosteroids combined with bronchodilators can reduce the frequency of exacerbations and slow the decline in quality of life. In patients with exacerbations, inhaled corticosteroids improve pulmonary function, and the results are additive to those achieved with long-acting bronchodilators. Inhaled corticosteroids, although poorly absorbed, probably do contribute to steroid side effects such as cataracts, capillary fragility, and osteoporosis in susceptible individuals. High doses of inhaled corticosteroids are associated with increased risk of pneumonia.^{60,61} In most cases, the risk is low compared to the benefit of treatment, but it is prudent to prescribe the lowest effective dose.

Adverse effects of inhaled therapy can occur. Inhaled anticholinergic agents are generally very safe. They may lead to an increased frequency of supraventricular arrhythmias, acute urinary retention in those with bladder outlet obstruction, or acute narrow-angle glaucoma if sprayed in the eye. β-Agonists, both short acting and long acting, may lead to side effects such as tremor, tachycardia, or hypokalemia.

Inhaled agents are administered by metered-dose inhaler (MDI), dry powder inhaler (DPI), or soft-mist inhaler (SMI), or as a nebulized solution. The selection of route of administration is made by cost and convenience of the device because all are similarly effective if used properly. There are several forms of DPI, some more intuitive to use than others, so specific instruction and demonstration is

required by most patients. Because DPIs may require a high inspiratory flow, some authorities recommend screening patients with peak inspiratory flow meters before prescribing a DPI.⁶² Nebulizers are easier for patients to coordinate, but each treatment takes longer to complete, and they require additional effort to maintain cleanliness. Although nebulized medications are more expensive overall, the cost of the medication is often borne by insurance, so patients may prefer nebulizers for financial considerations.

Adherence with inhaled medication, particularly when it does not provide immediate symptom relief, is poor. Typically, about half of patients do not collect or use their medication in the dose or quantity prescribed.⁶³ Reasons for this include a lack of understanding of the role of the medication, failure of the medication to provide meaningful benefit, complexity of the treatment program, and cost of the treatment. Many patients do not want to confide poor adherence to their physician, so it is important for the physician to ascertain this information in a way that does not interfere with the relationship with the patient. For example, a physician could inquire, “It is often difficult for patients to remember to take all of their medications. Has this been a problem for you?” or “Are you able to afford all your medication?” or “Do you think that your medicines are working for you?” If nonadherence is a problem, the treating physician can undertake actions to improve adherence, such as simplification of the medication program, education about the benefits of treatment, linking drug use to established habits such as meals or tooth brushing, or prescribing less costly drugs.

Proper use of MDIs is difficult for many patients to learn and retain. Repeated review and training of patients in MDI use is an important component of treatment of COPD and asthma. The inhaler should be held about 4 cm from the mouth to minimize deposition of larger droplets in the mouth. The patient should exhale to FRC and take a slow inhalation to TLC over about 5 seconds. The slow inhalation diminishes impaction of particles in the mouth and larynx. At the initiation of inspiration, the patient should actuate the MDI one time. After full inspiration, the patient should hold the breath for about 10 seconds to permit settling of particles in the distal airspaces. If the patient finds that hoarseness or mouth irritation occurs with inhaler use, this can often be corrected by use of a spacer, slowing the rate of inspiration, and rinsing the mouth after each inhaler use. Waiting a period of time between inhalations or between different MDIs is sometimes recommended for optimal effect, but the benefit is small compared with the inconvenience and risk of worsening adherence. Therefore, it is usually appropriate to permit the patient to take additional inhalations as soon as he or she has rested a few seconds.

If the patient has difficulty coordinating the actuation of the MDI with inspiration, a spacer device or holding chamber can be used. This device is placed directly in the mouth and the MDI is actuated prior to inspiration. DPIs usually require less coordination than MDIs, but there are many different devices, some rather complicated to use. Very frail patients may not have adequate inspiratory flow to effectively use a DPI. Therefore, each device requires individual instruction and repeated review of technique.⁶⁴ (For a compendium of patient instructions, see www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Educational-Video-Series.aspx)

Roflumilast is a highly specific inhibitor of phosphodiesterase 4, which is a mild bronchodilator with anti-inflammatory properties. It is marketed in the United States for reduction of exacerbations of COPD in individuals with chronic bronchitis, FEV₁ <50% predicted, and increased exacerbation events.⁶⁵ Gastrointestinal side effects can be minimized by starting with a low dose and increasing as tolerated. Because roflumilast causes weight loss in overweight patients and improves glycemic control in type 2 diabetics, it is particularly useful in these individuals.⁶⁶

Oral corticosteroids are effective for treatment of COPD exacerbations. About 10% to 20% of chronic symptomatic patients show substantial short-term improvement in pulmonary function, but it is not possible to identify these patients based on clinical characteristics alone. Because of the well-defined long-term adverse effects of systemic corticosteroids, and the ill-defined long-term benefits, most patients should not be maintained on long-term oral or systemic corticosteroids. Patients with COPD who are on chronic corticosteroids can most often taper the dose at the equivalent rate of 5 mg of prednisone per week, and exclusively reserve their use for exacerbations. Long-term low doses of oral corticosteroids are occasionally needed by patients who cannot afford or tolerate inhaled agents, and who suffer frequent exacerbations. Patients on long-term systemic steroids who are at high risk for osteoporosis should be considered for prophylactic treatment with bisphosphonates and should be instructed about the need for stress-dose steroids for acute illnesses.

Long-term macrolides, which have immunomodulatory as well as antibiotic properties, have been demonstrated to reduce the frequency of exacerbations in patients susceptible to frequent exacerbations.⁶⁷ These agents can be used in patients who still have exacerbations despite maintenance treatment with bronchodilators and inhaled steroids. It remains an unsettled question whether treatment with macrolides or roflumilast is superior for preventing severe exacerbations. In secondary analyses, the benefit of azithromycin appears to be present in former smokers, with minimal exacerbation reduction in current smokers.

Mucolytic agents to control mucus hypersecretion with the use of expectorants and physical means such as high-frequency chest wall oscillation or a flutter valve is not of proven benefit in improving lung function, although symptoms are sometimes improved. N-acetylcysteine, a mucolytic with antioxidant properties, does not alter the decline in FEV₁. However, antioxidant mucolytics, such as N-acetylcysteine or carbocysteine, may have a role in reducing exacerbations.^{68,69}

Opiates can be effective in the management of severe dyspnea related to COPD. Given differential response to these therapies, as well as the associated potential for respiratory depression, short-acting and low-dose preparations should be initially used. While typically associated with severe, end-stage management in the hospice setting, short-acting opiates can be considered in patients with less severe lung impairment but symptomatic dyspnea refractory to pharmacotherapy, oxygen supplementation, and rehabilitation.⁷⁰

■ Exercise and Rehabilitation

Regular, prudent, self-directed exercise is recommended for all individuals with COPD to prevent the muscle deconditioning that often accompanies the disorder. Individuals should be encouraged to perform at least 20 to 30 min of constant low-intensity aerobic exercise such as walking at least three times per week. Even the most severely impaired patients with COPD can usually attain an exercise regimen of 30 min of walking at 1 mph (i.e., one-half mile in 30 min). It is important to instruct patients that they should exercise to a level of dyspnea that is tolerable for the entire exercise period. Patients should understand that dyspnea, by itself, is not injurious to the heart or lungs, but patients should pace themselves to avoid severe dyspnea that disrupts activity, can lead to panic reactions, and is distressing to onlookers. Patients who demonstrate desaturation with exertion may be prescribed supplemental oxygen for exercise on an individualized basis. Many patients, particularly those with marked hyperinflation, find that they can ambulate better with the use of a rolling walker that supports the arms, improving the mechanical advantage of the accessory muscles in the neck. Initiation and maintenance of an exercise program as well as educational materials are increasingly available on telehealth platforms with internet connections.

Formal in-person rehabilitation programs offer a comprehensive approach to exercise training, patient education, nutritional counseling, group support, and psychological support that cannot be efficiently provided in the physician's office. Rehabilitation programs are established as an effective component of COPD management and should be offered to patients who have substantial limitation in daily activities. After hospitalization for COPD exacerbation, enrollment in pulmonary rehabilitation is associated with reduced mortality.⁷¹ A detailed discussion of rehabilitation is provided in Chapter 42.

■ Nutritional Support

About 25% to 40% of patients with COPD show evidence of nutritional depletion. Reasons for this include increased resting metabolic demands, inadequate caloric intake due to dyspnea and anorexia, and possibly elaboration of cachexia-associated inflammatory cytokines such as TNF- α , IL-1, and IL-6. Patients with a BMI of less than 90% of normal have increased mortality and decreased exercise capacity. Muscle wasting and loss of bone mass may be present even in patients who have normal BMI.⁷² Although clinical trials of nutritional supplementation have been disappointing, it is prudent to monitor body weight in patients with COPD and encourage caloric supplementation as needed since those patients who do gain weight show improved survival.⁷³ High-fat diets have the theoretical advantage of offering higher caloric content with

lower CO₂ production than high-carbohydrate diets, but there is no convincing evidence that this strategy is clinically superior to a well-balanced diet. For patients with less advanced disease, a balanced diet with avoidance of overweight or underweight is a rational goal. Particularly, patients with mild to moderate disease who quit smoking tend to gain excessive weight, which might adversely affect lung function.⁷⁴

■ Sleep Disorders in COPD

Sleep disturbances, including insomnia and daytime hypersomnolence, are common symptoms in patients with COPD, and are often overlooked because of the focus on breathlessness and exercise intolerance.⁷⁵ The causes for sleep symptoms are multifactorial and include anxiety, depression, resting hypoxemia, nocturnal bronchospasm, sleep apnea, and nocturnal oxygen desaturation (NOD). Patients with COPD often relate insomnia to a fear of suffocation or death during sleep, a situation that may respond to repeated reassurance, cognitive therapy, or small doses of hypnotics, anxiolytics, or antidepressants. Patients with resting hypoxemia treated with low-flow nasal oxygen often report improved sleep quality. Nocturnal bronchospasm, more common among those with an asthmatic component to their disease, may respond to longer-acting bronchodilators, or rearrangement of the dosing schedule to provide nocturnal coverage. In some cases, treatment for gastroesophageal reflux by elevation of the head of the bed and prescription of acid suppressant drugs can help.

Sleep apnea syndrome, probably not more common in COPD patients than the general community, has particularly severe complications in COPD. Patients with COPD and sleep apnea, the so-called overlap syndrome, are prone to develop pulmonary hypertension and daytime hypercapnia.⁷⁶ Accordingly, symptoms of sleep apnea such as snoring, intermittent nocturnal breathing, and daytime hypersomnolence should be sought in patients with COPD. If present, then formal sleep studies and treatment with continuous positive airway pressure (CPAP) are indicated. NOD is common during rapid eye movement sleep in patients with COPD. The causes are not entirely understood, but contributing factors include hypoventilation, ventilation–perfusion mismatch, respiratory muscle dysfunction, and increases in upper airway resistance. NOD is thought to be associated with poorer sleep quality and pulmonary hypertension. It is controversial whether NOD is associated with poorer survival. Randomized trials have shown inconclusive results about the benefit of treating NOD with supplemental oxygen.⁷⁷ There is, however, an increasing body of evidence that patients with hypercapnia have improved survival and fewer hospitalizations if treated with noninvasive ventilation at night.⁷⁸ Although evidence is limited, it is currently recommended that patients with chronic stable hypercapnia should use nocturnal noninvasive ventilation and should undergo sleep apnea screening.⁷⁹

Current guidelines do not recommend that all patients with COPD have nocturnal oxygen monitoring, nor do they recommend treatment with supplemental oxygen or nocturnal ventilation if NOD is found. Many physicians, though, will prescribe these diagnostic studies and treatments for selected symptomatic patients, and most insurance companies will provide reimbursement for such treatment. Patients who have resting room air daytime hypoxemia should be prescribed nocturnal oxygen at the same flow rate as used during the day, and it is usually not necessary to monitor nocturnal oxygen saturation in such patients.

■ Management of Depression

Depression is a common comorbidity in individuals with COPD and is related to the lack of social support.⁸⁰ The recognition and treatment of depression is important as this comorbidity is associated

with poorer prognosis, increased risk of exacerbations, and poor health status. Although there is little evidence to suggest that depression should be treated differently in COPD patients, pulmonary rehabilitation has been shown to reduce depression with COPD.

■ Air Travel

Patients with COPD do not need to avoid air travel but must be aware of the medical and regulatory issues that are involved.^{81,82} Modern airplanes are pressurized to an equivalent altitude of approximately 5000 to 8000 ft but may, on occasion, pressurize to an equivalent altitude of 10,000 ft without providing emergency oxygen. Many patients with COPD who do not use sea-level oxygen can tolerate short flights without supplemental oxygen. As flight distance becomes longer, the flying altitude becomes higher and the cabin pressure becomes lower, so transcontinental or transoceanic flights should prompt medical advice. The general rule of thumb used by the commercial airline industry is that patients who can ambulate 50 m without stopping are safe for air travel. A more conservative approach is to estimate the Pa_{O₂} during air travel by performing a high-altitude simulation test (Chapter 31).

High-altitude simulation can be performed by administering 15% oxygen via a face mask or by using 100% nitrogen in a 40% Venturi mask.⁸³ If the oxygen saturation falls below 86% or 50 mm Hg, then supplemental oxygen is recommended. Resting arterial oxygen saturation by itself is not a reliable indicator of oxygen desaturation at altitude. However, one study showed that a resting sea-level SpO₂ >95% with a 6-minute walk test SpO₂ >84% was highly sensitive for establishing that patients were able to fly without supplemental oxygen.⁸⁴ If resting SpO₂ is <92% or 6-minute walk test SpO₂ is <84% then oxygen should be prescribed for air travel. Patients who use oxygen supplementation at sea level should increase their resting oxygen prescription by a flow rate of 2 L/min. Patients with COPD who engage in air travel should use a pulse oximeter to monitor their saturation during the flight and adjust oxygen supplementation accordingly, particularly with pulsed-dose oxygen where equivalent constant flow rates are inconsistent.

Airlines have inconsistent policies with respect to providing supplemental oxygen for travelers, so it is important to check with the airline service desk before booking travel. The United States Federal Aviation Administration has promulgated regulations that permit approved portable oxygen concentrators to be carried on board by passengers as personal luggage with a physician's statement of need. These may be rented from oxygen supply companies or specialized websites. For battery-driven portable oxygen concentrators, extra batteries should be carried aboard to accommodate delays in the flight or extended time in the air.

The COVID-19 pandemic has focused attention on the transmission of droplet-borne viral diseases during air travel, which can be injurious to people with COPD. Therefore, it is rational to recommend use of facemasks and good hand hygiene for air travel for all individuals who may be susceptible to viral infection.⁸⁵

■ Long-Term Oxygen Therapy

Oxygen treatment of resting severe daytime hypoxemia prolongs survival.^{86–88} Guidelines recommend prescribing long-term oxygen therapy (LTOT) for at least 15 h/day for adults with COPD who have severe chronic resting room air hypoxemia (defined as PaO₂ ≤55 mm Hg or SpO₂ ≤88%). Oxygen is usually administered by nasal cannula, with the flow rate adjusted to maintain a resting saturation >90%. The usual starting flow rate is 2 L/min, although some patients with severe hypercapnia require lower flows. Some patients, particularly those with concomitant interstitial pulmonary disease or cardiovascular disorders, require higher flow rates.

The most convenient and cost-effective oxygen source at home is usually a concentrator device that uses a molecular sieve to extract

oxygen from room air. For ambulation, small, compressed oxygen cylinders, portable concentrators, or liquid oxygen reservoirs that can be carried provide patients with the ability to leave their homes. Conserving devices, such as reservoirs or demand valves, permit portable ambulatory oxygen tanks to last up to 10 h. Compressed oxygen cylinders or liquid oxygen reservoirs should be provided by home oxygen companies to patients who use electrically driven oxygen concentrators for emergency use in the event of a power failure. Ideally, oxygen should be used constantly 24 h per day. At least 18 h of oxygen per day, however, has been shown to have substantial benefit over 12 h per day. If continuous oxygen supplementation is prescribed following an exacerbation of COPD, it is recommended to check arterial oxygen levels in 6 weeks, as many patients will no longer require oxygen.

Nasal drying or congestion is a common symptom for those who use continuous oxygen. This may be alleviated to some extent by alternating the nasal cannula from one nostril to the other or placing it in the mouth for periods. Copious watery nasal secretions often respond well to ipratropium nasal spray, and dry, crusted nasal mucosa is treated with hourly instillations of saline nasal spray.

Smoking or exposure to any open flame is prohibited by the danger of fire and airway burns in those who use oxygen. This is a surprisingly common cause of burns in the United States, with estimates that up to 50% of patients on oxygen continue to smoke to some extent.⁸⁹ Accordingly, it is safer to counsel patients to discontinue oxygen while smoking or cooking over an open flame if they insist on doing these activities. Patients at particular risk are those who live alone, have cognitive impairment, and do not have functioning smoke detectors.

Ambulatory oxygen, although not shown to improve survival, may be provided for patients who desaturate with exertion. Some, but not all, patients show improved exercise capacity and reduced breathlessness. Patients with exercise desaturation or moderate levels of hypoxemia do not, however, benefit in terms of increased survival or decreased hospitalizations.⁹⁰ There is good evidence that oxygen supplementation during exercise training may benefit COPD patients who do not have exercise desaturation by reduction in minute ventilation and decreased dynamic hyperinflation.⁹¹ However, in sham-controlled clinical trials where oxygen treatment does not improve exercise intensity, there is no added training benefit.^{92,93} Therefore, the recommendation for oxygen during exercise training should be individualized based on patient preference and shared decision-making with the provider.

COMPLICATIONS

A variety of respiratory and cardiac complications may be seen in COPD and are discussed below.

COPD Exacerbations

Exacerbations are characterized by worsening cough, dyspnea, and sputum production beyond normal day-to-day variation. These exacerbations are associated with acute deterioration of lung function during the exacerbation and may also accelerate lung function decline. Acute exacerbations of COPD are a major cause of hospitalization, healthcare costs, morbidity, and mortality in COPD. Exacerbations have been associated with respiratory viral infections including rhinovirus, respiratory syncytial virus, influenza, adenovirus, and metapneumovirus. Bacterial infections or superinfections are also associated with COPD exacerbations. The most frequent pathogens are *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. In patients who have been previously treated frequently with antibiotics, gram-negative bacteria also may be present. Severe air pollution, especially particulates, sulfur

TABLE 40-8 Indications for Hospitalization in COPD

| Indications for Hospital Assessment or Admission for COPD Exacerbation |
|---|
| Sudden onset of new or severe symptoms (e.g., dyspnea) |
| Inability to sleep or eat because of dyspnea |
| Severe or very severe underlying COPD |
| Onset of new physical findings (e.g., edema, cyanosis, change in mental status) |
| Failure to respond to initial medical treatment |
| Associated comorbidities (e.g., cardiac, renal, hepatic failure, diabetes) |
| Diagnostic uncertainty (e.g., suspected pneumonia or pulmonary embolism) |
| Frailty or dementia |
| Inadequate home or social support |
| History of poor adherence with treatment |
| Indications for ICU Admission for COPD Exacerbation |
| Severe dyspnea unresponsive to initial treatment |
| Change in mental status (e.g., confusion, lethargy, coma) |
| Persistent or worsening hypoxemia, hypercapnia, or respiratory acidosis |
| Need for sedation or narcotic pain control |
| Need for mechanical ventilation |
| Need for hemodynamic monitoring |

Data from The 2021 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD).

dioxide, ozone, and nitrogen dioxide have been associated with elevated risk for hospitalization due to COPD. On average, patients with COPD have two to three exacerbations per year, but there is wide variation, and the frequency of exacerbations is only roughly correlated with severity of airflow obstruction. The best predictor of future exacerbations is a past history of frequent exacerbations, and these are more common in patients with chronic cough and sputum production.⁹⁴ Only half of COPD exacerbations come to the attention of treating physicians, and many of these eventually resolve without specific treatment. The management of these exacerbations depends upon the severity. Indications for hospital evaluation or hospitalization are listed in Table 40-8. Arterial blood gas studies and chest radiographs are useful for evaluating etiology and severity of acutely ill patients. Spirometry during the acute exacerbation is usually not helpful in predicting the severity or duration of the exacerbation.

For patients treated at home, increasing the frequency and intensity of inhaled short-acting bronchodilators for several days is effective in mild exacerbations. A hand-held inhaler and spacer are usually effective, but a nebulizer may be needed for those who cannot coordinate well or who have severe dyspnea. Increasing dyspnea accompanied by a change in the quantity or color of phlegm is usually an indication of bacterial infection and should prompt initiation of antibiotics. When readily available, C-reactive protein (CRP) levels are helpful in guiding antibiotic prescription.⁹⁵ The choice of antibiotic is determined by severity of the underlying disease, resistance patterns of likely pathogens, and likelihood of treatment failure (Table 40-9). For those not responding to treatment, the antibiotic should be tailored based on sputum cultures.

TABLE 40-9 Antimicrobial Treatment of COPD Exacerbations

| |
|---|
| First Line |
| Amoxicillin 500–875 mg PO TID |
| Doxycycline 100 mg PO BID |
| Azithromycin 500 mg, then 250 mg PO QD × 4 d |
| Alternatives |
| Amoxicillin/clavulanate 875 mg PO BID |
| Clarithromycin 500 mg PO BID |
| Second-generation cephalosporins |
| Previous antibiotics or known gram-negative pathogens |
| Levofloxacin 500–750 mg PO QD × 7 d |
| Ciprofloxacin 500 mg PO QD × 7 d |

A course of corticosteroids, equivalent to 30 to 60 mg of prednisone for 5 to 10 days, will shorten the duration of symptoms for patients with exacerbations managed as outpatients.^{96–98} For patients admitted to the hospital, intensification of inhaled bronchodilator treatment, systemic corticosteroids, and antibiotics are administered.⁹⁹ Controlled oxygen supplementation should be provided at the lowest level needed to reverse hypoxemia and minimize the induction of hypercapnia. The selection of the oral or intravenous route for antibiotics and corticosteroids is determined by the severity of the illness and the ability of the patient to tolerate oral medication. Evaluation for the cause of the exacerbation does not have to be extensive if it responds to initial treatment and conforms to the patient's usual exacerbation pattern. Sputum culture for resistant bacterial strains, a chest radiograph for exclusion of pneumonia and pneumothorax, and an electrocardiogram for exclusion of myocardial ischemia and arrhythmia are useful tests in all hospitalized patients. Echocardiography for assessment of ventricular function, and D-dimer, Doppler venous flow studies, radionuclide, or CT lung imaging for evaluation of pulmonary thromboembolism need to be performed in selected cases. Usually, a 5- to 14-day course of steroids is sufficient for hospitalized patients.

Treatment in an intensive care setting should be undertaken for patients with severe exacerbations or those who require more constant attention (Table 40-8). For patients with respiratory failure, noninvasive mask ventilation has proved to be an effective strategy to avert endotracheal intubation, shorten duration of illness, and improve outcomes.¹⁰⁰ Attention needs to be paid to selecting and fitting a comfortable well-sealed mask, and providing a ventilator that minimizes the patient's work of breathing and triggering effort. When noninvasive mask ventilation is not successful in sustaining ventilation, or the patient is too ill to use the mask, endotracheal intubation and mechanical ventilation are needed to treat respiratory failure. The mechanical ventilator should be set to provide minute ventilation that does not overventilate the patient and cause alkalemia, which may ultimately impede liberation from the ventilator. The inspiratory flow rates and inspiratory to expiratory time ratios should be adjusted to provide a prolonged duration of expiration to minimize dynamic hyperinflation (auto-PEEP), which can lead to dyspnea, coordination, and barotrauma. Weaning and liberation from mechanical ventilation can be hindered by anxiety, oversedation, mucus secretions, intravascular volume overload, myocardial ischemia, or respiratory muscle deconditioning. A hospitalization for COPD exacerbation should be considered a sentinel health event. Patients hospitalized for COPD exacerbation have a 25% 1-year mortality, with patients requiring mechanical ventilation having even poorer outcomes—with about a 40% 1-year mortality for those who survive the hospitalization.^{101,102}

Given the clinical impact of a hospitalized exacerbation, all COPD patients should have their maintenance COPD regimen reassessed at time of discharge for appropriate modifications and have close outpatient follow-up after discharge.

■ Pneumothorax

Smoking-related emphysema is thought to be the most common cause for secondary spontaneous pneumothorax.¹⁰³ A pneumothorax can either cause an acute symptomatic exacerbation of COPD from rupture of a bleb or may occur during the course of an exacerbation as a consequence of hyperinflation or mechanical ventilation. Because this is a life-threatening but quickly treatable cause for worsening respiratory failure in COPD, it should always be considered in the differential diagnosis for worsening dyspnea in COPD. The physical examination can be misleading because diminished breath sounds are a component of COPD. Imaging studies are usually diagnostic, but at times it can be difficult to distinguish a pneumothorax from an overdistended bulla. If the patient's clinical situation can tolerate it, imaging with inspiratory and expiratory views or chest CT can be helpful. In the intensive care unit, upright and cross-table lateral views sometimes show mobility of the pleural air.

Urgent treatment for the patient in extremis is performed by aspirating the pleural space at the second intercostal space anteriorly in the midclavicular line. Definitive emergency treatment is placement of a thoracostomy tube, which should be done with care to avoid laceration of a bulla and creation of a bronchopleural fistula. In patients with advanced COPD, recurrence of a pneumothorax is common and can be life-threatening, so definitive pleural sclerosis with surgical or medical thoracoscopy should be considered. If there is a persistent bronchopleural fistula, surgical intervention or endobronchial valve insertion may hasten recovery.¹⁰⁴

■ Cor Pulmonale

Pulmonary hypertension and consequent right ventricular failure, *cor pulmonale*, are usually the consequence of chronic alveolar hypoxia, with secondary contributions from destruction of the alveolar capillary bed, lung hyperinflation, and increased blood viscosity.¹⁰⁵ Diagnosis of pulmonary hypertension and right ventricular failure can be difficult, as physical findings of venous engorgement and right ventricular hypertrophy and dilation are late signs. Peripheral edema is poorly correlated with resting right atrial pressure and may reflect fluid retention from activation of the renin–angiotensin–aldosterone system. Functional imaging studies including echocardiography or cardiac MRI are more probative for evaluation of right ventricular function. Doppler echocardiographic measures of pulmonary artery systolic pressure correlate poorly with severity of pulmonary hypertension by right heart catheterization.¹⁰⁶ In situations where *cor pulmonale* is not associated with chronic hypoxemia, investigations for pulmonary thromboembolism and sleep apnea overlap may be helpful. Once *cor pulmonale* is present, survival is diminished. If the pulmonary artery pressure exceeds 25 mm Hg, the average 5-year survival is diminished by 50%.^{107,108}

The primary treatment of *cor pulmonale* consists of continuous oxygen to overcome hypoxemia and diuretic to optimize volume status. Calcium channel blockers and other vasodilators can dilate the pulmonary circulation, but they worsen hypoxemia and their benefit is not established. Traditionally polycythemia was thought to be common and an indication of poor prognosis in chronically hypoxic patients with COPD, but recent cohort studies indicate that polycythemia is infrequent and has an uncertain effect on outcomes.¹⁰⁹

■ Supraventricular Arrhythmias

Supraventricular tachyarrhythmias are common in patients with COPD as a consequence of right atrial enlargement, increased

endogenous adrenergic tone, hypoxemia, and drug treatment—specifically bronchodilators. Treatment is similar to that in non-pulmonary patients; however, the presence of COPD should not prevent evaluation for treatable causes of arrhythmias such as pulmonary embolism, hyperthyroidism, or valvular heart disease, which may be difficult to diagnose in COPD patients.

■ Hypercapnia

Chronic hypercapnia secondary to alveolar hypoventilation can be considered an adaptive response to obstructive lung disease by decreasing the work of breathing, preventing respiratory muscle fatigue, and allowing a diminished sensation of dyspnea. The adverse effect of chronic hypercapnia is the development of alveolar hypoxia and consequent pulmonary hypertension. Accordingly, the approach to chronic hypercapnia is the use of supplemental oxygen in controlled concentrations. In patients who are very sensitive to oxygen, it is preferable to provide oxygen in controlled concentrations with Venturi masks rather than nasal cannula.

Nocturnal ventilation has been effective in reducing daytime hypercapnia in patients with neuromuscular disease and kyphoscoliosis. Nocturnal noninvasive ventilation may be used to normalize nocturnal hypercapnia in patients with stable chronic hypercapnia. Investigation for concomitant sleep apnea syndrome is recommended.^{79,110}

ADVANCED TREATMENTS

For patients who have far-advanced disease evidenced by either severe breathlessness or short life expectancy, more aggressive treatments should be considered. Undertaking these treatments requires thoughtful consideration by patients and their families, and frank discussion of the risks and benefits by the medical caregivers.

■ Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) is a surgical procedure that involves stapled resection of 20% to 30% of the lung bilaterally, usually from the apices. The procedure is equally safe and effective, done by median sternotomy or video-assisted thoracoscopy (VATS). The theory behind this procedure is that the remaining lung expands to fill the thorax, thereby increasing its elastic recoil pressure, which improves expiratory airflow. The reduction of lung volume permits the diaphragm to attain a more normal, domed configuration, which improves its mechanical efficiency. Moreover, the preferential removal of unventilated bullae reduces residual volume, permitting an increase in the vital capacity. While some patients show substantial physiologic and symptomatic improvement following LVRS, many do not.¹¹¹ Generally, LVRS should not be done on patients with an FEV₁ less than 20% predicted and either diffusing capacity less than 20% predicted or diffuse homogeneous emphysema on HRCT, because these patients have high surgical mortality.¹¹² The group of patients who fare best with LVRS are those who have emphysema predominantly in the upper lung zones and low exercise capacity despite pulmonary rehabilitation. These patients have improved survival after LVRS and show improved functional status and quality of life. Conversely, patients without upper lobe predominance (i.e., lower lobe emphysema or homogeneous emphysema), and who have adequate exercise capacity after rehabilitation, have worse outcomes after LVRS.

Surgical resection of a single large bulla is rarely indicated for treatment of COPD. Isolated giant bullae are usually the result of an expanding congenital cyst. The generally accepted indication for resection of a single large bulla is that it occupies more than one-third of the hemithorax and causes compression of normal lung. Some believe that a preserved D_{CO} is an indicator of those most likely to improve following a bullectomy.

Nonsurgical approaches to lung volume reduction using a variety of techniques to induce atelectasis of a target lobe have generally supplanted surgical lung volume reduction. Placement of endobronchial valves in regions of lung with severe emphysema without collateral ventilation can lead to clinically meaningful improvement in symptoms.^{113,114} Because pneumothorax is common after these procedures, patients are often observed in hospital for several days after the procedure. Patients who achieve complete atelectasis of the target lobe have the best symptomatic and survival outcomes.¹¹⁵

■ Lung Transplantation

In younger patients with advanced disease, lung transplantation should be a treatment consideration. Criteria for lung transplantation referral in patients with COPD are an FEV₁ below 25% predicted, BODE index greater than 5, hypercapnia, resting hypoxemia, secondary pulmonary hypertension, and accelerated decline in FEV₁ in patients under the age of 65 years.¹¹⁶ For additional information see Chapter 106.

■ Chronic Ventilator Support

Some patients remain on long-term ventilator support following an episode of acute respiratory failure. Most often these patients are treated in a long-term ventilator unit, but some can be managed at home with adequate support. In some cases, the goal of long-term ventilator support is to provide rehabilitation via respiratory care, nutrition, and exercise to eventually be liberated from the ventilator entirely or for substantial portions of the day. In other cases, the goal of care is to provide comfort and support for terminal care without attempts at rehabilitation. Whatever the goal, a coordinated team of physicians, respiratory therapists, physical therapists, nutritionists, social workers, psychologists, and nurses are needed to undertake the care of these patients.

The treatment of long-term ventilator patients differs from the treatment of acute respiratory failure in the intensive care unit. Ventilators are less sophisticated in terms of modes of ventilation and monitoring, but more portable. Ventilation is often performed with an uncuffed tracheostomy with an air leak to avoid complications at the cuff site. Sufficiency of ventilation is judged by noninvasive measures of oxygenation and patient comfort. Narcotics in small doses are administered for relief of dyspnea. Diagnostic studies and invasive testing are performed less frequently than in critical care units. Although the care in long-term ventilator units is complex and expensive, the quality of life experienced by patients in chronic ventilator units is similar to that of patients confined to a bed-and-chair existence by other chronic maladies. The survival of patients with COPD on long-term mechanical ventilation is less than 3 years on average and is less than those on such treatment for neuromuscular diseases, in part, because of their older age and comorbidities.¹¹⁷

CONCLUSIONS

COPD develops insidiously. However, the disease can be easily detected with simple spirometric testing before symptoms occur, and cessation of smoking can slow or even halt the disease progression and prolong survival. Once the disease is symptomatic, a coordinated, comprehensive, and individualized approach to treatment, both pharmacologic and nonpharmacologic, can increase functional status, prevent complications, and improve the quality of life. Exacerbations of COPD can range from those that are nuisances to those that are life-threatening, but treatment can shorten the duration of illness and improve outcomes. In advanced disease, treatments including surgical and bronchoscopic approaches are directed toward relief of symptoms. Thus, although there is certainly need for improvement in our treatment of symptomatic COPD, current treatments are effective, and a nihilistic attitude is not warranted.

DISCLOSURES

Disclosure of financial conflicts: During the preceding 5 years, Dr. Wise has received fees for consultation or support of research from the following companies: AbbVie, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Chiesi, ChimiRix, Circassia, Contrafect, FSD Pharma, Galderma, Genentech, GlaxoSmithKline, Kamada, Kinevant, Kiniksa, Merck, Mylan, Novartis, Pfizer, Polarean, Pulmonx, Puretech, Sanofi, Roche, Theravance, Verona.

During the preceding 5 years, Dr. Drummond has received fees for consultation or support of research from the following companies: AstraZeneca, Boehringer-Ingelheim, Enterprise Therapeutics, GlaxoSmithKline, Lupin Pharmaceuticals, Midmark, NovaVax, Parion, Polarean, and Teva, Theravance Biopharma/Mylan.

REFERENCES

- The 2021 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). www.goldcopd.org/. Accessed March 5, 2021.
- Smith LJ. The lower limit of normal versus a fixed ratio to assess airflow limitation: will the debate ever end? *Eur Respir J*. 2018;51(3):1800403.
- Han MK, Agusti A, Celli BR, et al. From GOLD 0 to pre-COPD. *Am J Respir Crit Care Med*. 2021;203(4):414–423.
- Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645–2653.
- Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med*. 2015;373(2):111–122.
- Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. *N Engl J Med*. 2019;381(13):1248–1256.
- Drummond MB, Hansel NN, Connell JE, et al. Spirometric predictors of lung function decline and mortality in early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;185(12):1301–1306.
- Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med*. 2011;365(13):1184–1192.
- Anthonisen NR, Connell JE, Murray RP, et al. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med*. 2002;166(5):675–679.
- Anthonisen NR, Connell JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA*. 1994;272(19):1497–1505.
- Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005;142(4):233–239.
- U.S. Preventive Services Task Force. Screening for Chronic Obstructive Pulmonary Disease: Recommendation Statement. *JAMA*. 2016;315(13):1372–1377.
- Zhou Y, Zhong NS, Li X, Chen S, et al. Tiotropium in early-stage chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377(10):923–935.
- Decramer M, Celli B, Kesten S, et al. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet*. 2009;374(9696):1171–1178.
- Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med*. 2008;178(4):332–338.
- O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2006;3(2):180–184.
- Donahoe M, Rogers RM, Wilson DO, Pennock BE. Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1989;140(2):385–391.
- Rawal G, Yadav S. Nutrition in chronic obstructive pulmonary disease: a review. *J Transl Int Med*. 2015;3(4):151–154.
- Badgett RG, Tanaka DJ, Hunt DK, et al. Can moderate chronic obstructive pulmonary disease be diagnosed by historical and physical findings alone? *Am J Med*. 1993;94(2):188–196.
- Sarkar M, Bhardwaz R, Madabhavi I, Modi M. Physical signs in patients with chronic obstructive pulmonary disease. *Lung India*. 2019;36(1):38–47.
- Straus SE, McAlister FA, Sackett DL, Deeks JJ. Accuracy of history, wheezing, and forced expiratory time in the diagnosis of chronic obstructive pulmonary disease. *J Gen Intern Med*. 2002;17(9):684–688.
- Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis*. 2016;3(3):668–682.
- Chapman KR, Burdon JG, Piiulainen E, et al. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind placebo-controlled trial. *Lancet*. 2015;386(9991):360–368.
- Morris A, George MP, Crothers K, et al. Lung HIV Study. HIV and chronic obstructive pulmonary disease: is it worse and why? *Proc Am Thorac Soc*. 2011;8(3):320–325.
- Drummond MB, Kirk GD, Astemborski J, et al. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. *Thorax*. 2012;67(4):309–314.
- COPD Assessment Test. <https://www.catestonline.org/>. Accessed April 6, 2021.
- Jones PW, Harding G, Wiklund I. Tests of the responsiveness of the Chronic Obstructive Pulmonary Disease (COPD) assessment TestTM (CAT) following acute exacerbations and pulmonary rehabilitation. *Chest*. 2012;142:134–140.
- Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl*. 2003;41:46s–53s.
- Lynch DA, Moore CM, Wilson C, et al. CT-based visual classification of emphysema: association with mortality in the COPDGene study. *Radiology*. 2018;288(3):859–866.
- Bhatt SP, Washko GR, Hoffman EA, et al. Imaging advances in chronic obstructive pulmonary disease. insights from the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) study. *Am J Respir Crit Care Med*. 2019;199(3):286–301.
- Casanova C, Cote C, de Torres JP, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171(6):591–597.
- Berry CE, Wise RA. Mortality in COPD: causes, risk factors, and prevention. *COPD*. 2010;7(5):375–382.
- Lipson DA, Crim C, Criner GJ, et al. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol

- in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2020;201(12):1508–1516.
34. Rabe KF, Martinez FJ, Ferguson G, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med.* 2020;383(1):35–48.
35. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest.* 2002;121(5):1434–1440.
36. Martinez FJ, Foster G, Curtis JL, et al. Predictors of mortality in patients with emphysema and severe airflow obstruction. *Am J Respir Crit Care Med.* 2006;173(12):1326–1334.
37. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350(10):1005–1012.
38. Puhan MA, Garcia-Aymerich J, Frey M, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet.* 2009;374(9691):704–711.
39. US Preventive Services Task Force. Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2021;325(3):265–279.
40. Lindson N, Thompson TP, Ferrey A, et al. Motivational interviewing for smoking cessation. *Cochrane Database Syst Rev.* 2019;7(7):CD006936.
41. Coggon D, Newman Taylor A. Coal mining and chronic obstructive pulmonary disease: a review of the evidence. *Thorax.* 1998;53(5):398–407.
42. Siddharthan T, Grigsby MR, Goodman D, et al. Association between household air pollution exposure and chronic obstructive pulmonary disease outcomes in 13 low- and middle-income country settings. *Am J Respir Crit Care Med.* 2018;197(5):611–620.
43. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet.* 2009;374(9691):733–743.
44. Johnson MK, Smith RP, Morrison D, et al. Large lung bullae in marijuana smokers. *Thorax.* 2000;55(4):340–342.
45. Tashkin DP. Marijuana and lung disease. *Chest.* 2018;154(3):653–663.
46. Walters JA, Tang JN, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2017;(1):CD001390.
47. Kopsaftis Z, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev.* 2018;6(6):CD002733.
48. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. *Am J Respir Crit Care Med.* 1998;158(1):49–59.
49. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis.* 2016;3(3):668–682.
50. Chapman KR, Burdon JG, Piitulainen E, et al. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;386(9991):360–368.
51. Cooper CB, Celli BR, Jardim JR, et al. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. *Chest.* 2013;144(2):490–497.
52. Ram FS, Sestini P. Regular inhaled short acting beta2 agonists for the management of stable chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *Thorax.* 2003;58(7):580–584.
53. Appleton S, Poole P, Smith B, et al. Long-acting beta2-agonists for chronic obstructive pulmonary disease patients with poorly reversible airflow limitation. *Cochrane Database Syst Rev.* 2002;(3):CD001104.
54. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. *Cochrane Database Syst Rev.* 2018;12(12):CD012620.
55. Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis. *Eur Respir J.* 2018;52(6):1801586.
56. Nici L, Mammen MJ, Charbek E, et al. Pharmacologic management of chronic obstructive pulmonary disease. An Official American Thoracic Society Clinical practice guideline. *Am J Respir Crit Care Med.* 2020;201(9):e56–e69.
57. Wise R, Connell J, Weinmann G, et al. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med.* 2000;343(26):1902–1909.
58. Pauwels RA, Löfdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med.* 1999;340(25):1948–1953.
59. Pascoe S, Barnes N, Brusselle G, et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. *Lancet Respir Med.* 2019;7(9):745–756.
60. Drummond MB, Dasenbrook EC, Pitz MW, et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA.* 2008;300(20):2407–2416.
61. Dransfield MT, Crim C, Criner GJ, et al. Risk of exacerbation and pneumonia with single-inhaler triple versus dual therapy in IMPACT. *Ann Am Thorac Soc.* 2021;18(5):788–798.
62. Mahler DA, Halpin DMG. Peak inspiratory flow as a predictive therapeutic biomarker in COPD. *Chest.* 2021;160(2):491–498.
63. Nishi SPE, Maslonka M, Zhang W, et al. Pattern and adherence to maintenance medication use in Medicare beneficiaries with chronic obstructive pulmonary disease: 2008–2013. *Chronic Obstr Pulm Dis.* 2018;5(1):16–26.
64. Press VG, Arora VM, Trella KC, et al. Effectiveness of interventions to teach metered-dose and Diskus inhaler techniques. A randomized trial. *Ann Am Thorac Soc.* 2016;13(6):816–824.
65. Calverley PM, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet.* 2009;374(9691):685–694.
66. Wouters EF, Bredenbröker D, Teichmann P, et al. Effect of the phosphodiesterase 4 inhibitor roflumilast on glucose metabolism in patients with treatment-naïve, newly diagnosed type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2012;97(9):E1720–E1725.
67. Albert RK, Connell J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med.* 2011;365(8):689–698.
68. Zheng JP, Wen FQ, Bai CX, et al. PANTHEON study group. Twice daily N-acetylcysteine 600 mg for exacerbations of

- chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respir Med.* 2014;2(3):187–194.
69. Zheng JP, Kang J, Huang SG, et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. *Lancet.* 2008;371(9629):2013–2018.
 70. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMG, et al. Effect of sustained-release morphine for refractory breathlessness in chronic obstructive pulmonary disease on health status: a randomized clinical trial. *JAMA Intern Med.* 2020;180(10):1306–1314.
 71. Lindenauer PK, Stefan MS, Pekow PS, et al. Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries. *JAMA.* 2020;323(18):1813–1823.
 72. Machado FVC, Spruit MA, Groenen MTJ, et al. Frequency and functional translation of low muscle mass in overweight and obese patients with COPD. *Respir Res.* 2021;22(1):93.
 73. Schols AM, Wouters EF. Nutritional abnormalities and supplementation in chronic obstructive pulmonary disease. *Clin Chest Med.* 2000;21(4):753–762.
 74. Wise RA, Enright PL, Connell JE, et al. Effect of weight gain on pulmonary function after smoking cessation in the Lung Health Study. *Am J Respir Crit Care Med.* 1998;157(3 Pt 1):866–872.
 75. Budhiraja R, Siddiqi TA, Quan SF. Sleep disorders in chronic obstructive pulmonary disease: etiology, impact, and management. *J Clin Sleep Med.* 2015;11(3):259–270.
 76. Adir Y, Humbert M, Chaouat A. Sleep-related breathing disorders and pulmonary hypertension. *Eur Respir J.* 2021;57(1):2002258.
 77. Lacasse Y, Séries F, Corbeil F. Randomized trial of nocturnal oxygen in chronic obstructive pulmonary disease. *N Engl J Med.* 2020;383(12):1129–1138.
 78. Wilson ME, Dobler CC, Morrow AS, et al. Association of home noninvasive positive pressure ventilation with clinical outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA.* 2020;323(5):455–465.
 79. Macrea M, Oczkowski S, Rochwerg B, et al. Long-term non-invasive ventilation in chronic stable hypercapnic chronic obstructive pulmonary disease. An Official American Thoracic Society Clinical practice guideline. *Am J Respir Crit Care Med.* 2020;202(4):e74–e87.
 80. Turnier L, Eakin M, Woo H. The influence of social support on COPD outcomes mediated by depression. *PLoS One.* 2021;16(3):e0245478.
 81. Shrikrishna D, Coker RK. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. *Thorax.* 2011;66(9):831–833.
 82. Ergan B, Akgun M, Pacilli AMG, Nava S. Should I stay or should I go? COPD and air travel. *Eur Respir Rev.* 2018;27(148):180030.
 83. Vohra KP, Klocke RA. Detection and correction of hypoxemia associated with air travel. *Am Rev Respir Dis.* 1993;148(5):1215–1219.
 84. Edvardsen A, Akero A, Christensen CC, et al. Air travel and chronic obstructive pulmonary disease: a new algorithm for preflight evaluation. *Thorax.* 2012;67:964–969.
 85. De Angelis G, Lohmeyer FM, Grossi A, et al. Hand hygiene and facemask use to prevent droplet-transmitted viral diseases during air travel: a systematic literature review. *BMC Public Health.* 2021;21(1):760.
 86. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet.* 1981;1(8222):681–686.
 87. Jacobs SS, Krishnan JA, Lederer DJ, et al. Home oxygen therapy for adults with chronic lung disease. An Official American Thoracic Society Clinical practice guideline. *Am J Respir Crit Care Med.* 2020;202(10):e121–e141. Erratum in: *Am J Respir Crit Care Med.* 2021;203(8):1045–1046.
 88. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med.* 1980;93(3):391–398.
 89. Lindford AJ, Tehrani H, Sassoon EM, O'Neill TJ. Home oxygen therapy and cigarette smoking: a dangerous practice. *Ann Burns Fire Disasters.* 2006;19(2):99–100.
 90. Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med.* 2016;375(17):1617–1627.
 91. Emtner M, Porszasz J, Burns M, et al. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. *Am J Respir Crit Care Med.* 2003;168(9):1034–1042.
 92. Alison JA, McKeough ZJ, Leung RWM, et al. Oxygen compared to air during exercise training in COPD with exercise-induced desaturation. *Eur Respir J.* 2019;53:1802429.
 93. Rooyackers JM, Dekhuijzen PN, Van Herwaarden CL, et al. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *Eur Respir J.* 1997;10:1278–1284.
 94. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med.* 2010;363(12):1128–1138.
 95. Butler CC, Gillespie D, White P. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med.* 2019;381(2):111–120.
 96. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med.* 1999;340(25):1941–1947.
 97. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *JAMA.* 2013;309(21):2223–2231.
 98. Wedzicha JA, Miravitles M, Hurst JR, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2017;49(3):1600791.
 99. Wedzicha JA, Miravitles M, Hurst JR, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J.* 2017;49(3):1600791.
 100. Osadnik CR, Tee VS, Carson-Chahoud KV, et al. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Sys Rev.* 2017;7(7):CD004104.
 101. Lindenauer PK, Dharmarajan K, Qin L. Risk trajectories of readmission and death in the first year after hospitalization for

- chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2018;197(8):1009–1017.
102. Hajizadeh N, Goldfeld K, Crothers K. What happens to patients with COPD with long-term oxygen treatment who receive mechanical ventilation for COPD exacerbation? A 1-year retrospective follow-up study. *Thorax.* 2015;70(3):294–296.
103. MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax.* 2010;65(Suppl 2):ii18–ii31.
104. Giddings O, Kuhn J, Akulian J. Endobronchial valve placement for the treatment of bronchopleural fistula: a review of the current literature. *Curr Opin Pulm Med.* 2014;20(4):347–351.
105. Naeije R. Pulmonary hypertension and right heart failure in chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2005;2(1):20–22.
106. Fisher MR, Criner GJ, Fishman AP, et al. Estimating pulmonary artery pressures by echocardiography in patients with emphysema. *Eur Respir J.* 2007;30(5):914–921.
107. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J.* 2008;32(5):1371–1385.
108. Balasubramanian A, Kolb TM, Damico RL. Diffusing capacity Is an independent predictor of outcomes in pulmonary hypertension associated with COPD. *Chest.* 2020;158(2):722–734.
109. Cote C, Zilberberg MD, Mody SH, et al. Haemoglobin level and its clinical impact in a cohort of patients with COPD. *Eur Respir J.* 2007;29(5):923–929.
110. Ergan B, Oczkowski S, Rochwerg B, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur Respir J.* 2019;54(3):1901003.
111. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med.* 2003;348(21):2059–2073.
112. National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med.* 2001;345(15):1075–1083.
113. Criner GJ, Sue R, Wright S, et al. A multicenter randomized controlled trial of Zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). *Am J Respir Crit Care Med.* 2018;198(9):1151–1164.
114. Criner GJ, Delage A, Voelker K, et al. Improving lung function in severe heterogenous emphysema with the spiration valve system (EMPROVE). A multicenter, open-Label randomized controlled clinical trial. *Am J Respir Crit Care Med.* 2019;200(11):1354–1362.
115. Hopkinson NS, Kemp SV, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. *Eur Respir J.* 2011;37(6):1346–1351.
116. Siddiqui FM, Diamond JM. Lung transplantation for chronic obstructive pulmonary disease: past, present, and future directions. *Curr Opin Pulm Med.* 2018;24(2):199–204.
117. White AC. Long-term mechanical ventilation: management strategies. *Respir Care.* 2012;57(6):889–897.

CHAPTER 41

Cigarette Smoking, Smoking Cessation, and Electronic Cigarettes

Stephen R. Baldassarri

Stephen I. Rennard

INTRODUCTION

Native Americans discovered the use of the tobacco plant, *Nicotiana tabacum*, during antiquity. By the time Columbus arrived in America, tobacco use was widespread throughout the Western Hemisphere and was well integrated into Native American cultures. Production of tobacco and its trade represented a major economic activity in the pre-Columbian Americas. Early European explorers learned of the tobacco plant from Native Americans, and by the mid-17th century tobacco was widely used in Europe.

The most important, but not the only, active psychopharmaceutical drug contained in the leaves of the tobacco plant is nicotine.^{1,2} Nicotine is a major metabolic product of the tobacco plant, and it is likely that it evolved as a protection against insect predators, as nicotine is a potent insect neurotoxin.³ Interestingly, nicotine has been exploited in this regard as a commercial insecticide. Nicotine, however, is the major addicting substance in tobacco, although the addiction to tobacco is more complex than addiction to nicotine alone. Other psychoactive compounds also are present in tobacco smoke, including monoamine oxidase inhibitors.⁴ These may either have direct effects, interact with other psychoactive drugs, or both.^{1,2} In addition, conditioned behavior and social interactions are important drivers of smoking.⁵⁻⁸

Nicotine is a potent euphoriant. On a molar basis, nicotine is more active than such euphoria-inducing drugs as cocaine, amphetamine, or morphine.⁹ Nicotine elicits complex effects on the central nervous system (CNS), which are discussed in more detail below. Many of these effects, however, are perceived as desirable, accounting for the popularity of smoking. For example, nicotine ameliorates anxiety, reduces perception of pain,¹⁰ mitigates symptoms of depression,¹¹ and induces a sense of well-being⁹ while causing a state of arousal.¹² In contrast to many euphoriants that impair cognition, nicotine can improve task performance and attention time by measurable degrees in non-habituated individuals and may have beneficial effects on cognition.¹²

Despite its perceived benefits, smoking of tobacco has long been controversial. King James of England wrote in 1604 “[Smoking is] a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black stinking fume thereof, nearest resembling the horrible Stygian smoke of the pit that is bottomless.”¹³ The Surgeon General’s Report of 1964 outlined the convincing evidence for the health consequences of smoking.¹⁴ Since that time, there has been a gradual increase in efforts to control tobacco use and the associated health consequences. Changes in social attitude, public health efforts, and both pharmacologic and nonpharmacologic approaches have been developed that have meaningful benefits. The current chapter will focus on treatment designed to help a smoker achieve abstinence. An overview of the increasingly important topic of electronic cigarettes will conclude the chapter.

NICOTINE ADDICTION

Nicotine exerts its biologic effects on “nicotinic” receptors, a subset of cholinergic receptors, whose endogenous ligand is acetylcholine.^{15,16} Nicotinic receptors are homo- or heteropentamers that bind two ligand molecules and form an ion channel.¹⁷ In humans, 17 genes code for distinct component chains, resulting in a very large number of potential pentamers, although only a relatively few are believed to have a biologic role. In the brain, nine alpha and three beta receptors are expressed. However, the major receptors are composed of complexes $\alpha 4\beta 2$, $\alpha 3\beta 4$, and $\alpha 7$. The $\alpha 4\beta 2$ complex incorporates other subunits, particularly $\alpha 5$, $\alpha 6$, or $\beta 3$, and these may modulate the effects of ligands, including nicotine.¹⁷ The $\alpha 4\beta 2$ receptor is believed to be particularly important in the addicting effects of nicotine. Deleting the $\beta 2$ receptor in mice eliminates behavioral responses to nicotine, while mutations in the gene can result in markedly increased sensitivity to nicotine.¹⁸ The $\alpha 7$ receptor, for example, is believed to mediate some of the cognitive effects of nicotine, including sensory gating and learning.^{18,19} In contrast the muscarinic receptors, the other major class of cholinergic receptors, are single-chain G protein-coupled receptors. Nicotine has no effect on these receptors.

Nicotinic receptors are ion channels. Upon binding of nicotine, permeability of the channel is increased.¹⁵⁻¹⁸ For example, binding of nicotine to the $\alpha 4\beta 2$ allows influx of calcium. This, in turn, modulates release of neurotransmitters. It is likely that the behavioral responses to nicotine result from the actions of many neurotransmitters, but dopamine is believed to be a major mediator of nicotine effects. In this context, dopamine is a key mediator of pleasure and reward and is required for the reinforcing effects that lead to drug self-administration in animal models.²⁰ As such, dopaminergic signaling is believed to be key in the pathogenesis of many addictions and compulsive behaviors. Nicotine also modulates the release of other neurotransmitters, including glutamate and gamma-amino butyric acid (GABA). Interestingly, chronic administration of nicotine desensitizes neurons that release GABA, which inhibits dopamine release. In contrast, there is no desensitization of glutamate release, which augments dopamine release. Chronic nicotine exposure, therefore, can lead to further augmentation of dopamine release.^{21,22} Moreover, the CNS alterations that occur following nicotine administration can be very long lasting; for example, alterations in nicotine receptor levels in rats exposed in utero persist until adult life.²³ The adolescent brain may be particularly sensitive to long-term alterations induced by nicotine.²⁴ This may account for the sensitivity of adolescents to addiction. Persistent changes in the brain may also account for the observation that, even after achieving abstinence, a smoker is at risk for relapse and if relapse occurs, the smoker reverts to the previous “steady-state” habit much more rapidly than that habit developed initially.

Nicotine is contained in the leaves of the tobacco plant. Nicotine is a weak base and as a result will be charged in acidic environments. Many forms of tobacco, such as cigars and chewing tobacco, are alkalized, which results in uncharged nicotine that can be more readily absorbed through the buccal mucosa. Thus, cigar smokers do not have to inhale to achieve desired blood nicotine levels. The process of smoking a cigarette is more complex.²⁵ Air sucked through the burning end of a cigarette becomes heated. As the hot air passes down the bole of a cigarette, it causes the nicotine in the tobacco to vaporize. As the mixture cools, the nicotine condenses on smoke particles resulting in a nicotine aerosol. Conventional cigarettes have been designed so that the resulting particle size is ideal to reach the alveolar structures of the lung. Uncharged nicotine is lipid soluble and is rapidly absorbed from the alveolar gas into the

pulmonary capillary blood and then into the arterial circulation. Inhaled nicotine, therefore, reaches the brain in about half a circulation time or about 15 to 20 s. In its neutral form, nicotine readily crosses the blood–brain barrier and exerts its psychoactive effects. A cigarette, therefore, is a very effective means of delivering nicotine to the brain. It also allows a smoker to control the dose of delivered drug with considerable precision.

After absorption, nicotine distributes into various body pools. This results in a marked difference between arterial and venous nicotine levels and a rapid drop in nicotine levels upon completion of a cigarette.²⁶ Nicotine is then catabolized by several enzymes. The most important of these is CYP2A6, which oxidizes nicotine to cotinine and cotinine to hydroxycotinine.²⁷ Nicotine can also be oxidized by alternative CYP450 enzymes and may be inactivated and excreted by glucuronidation. Genetic variants in nicotine metabolizing enzymes can influence smoking behavior. In normal metabolizers, nicotine is cleared with a half-life of about 2 h. As a result, nicotine levels increase throughout the day for individuals who smoke steadily. The increase in nicotine levels can result in levels believed to fully saturate all nicotinic receptors.^{1,2} In this setting, it is likely that smoking behavior is more dependent on conditioned responses than on psychopharmacologic effects of nicotine. Conversely, nicotine levels fall at night. The drop in nicotine levels is thought to initiate the early stages of withdrawal. Importantly, the lower levels allow for nicotinic receptors to be in the unbound state. As a result, the first cigarette in the morning can have a large psychodynamic effect. This is well recognized by smokers who will often report that the “most enjoyable” cigarette is the first one smoked in the morning. In addition, the drop in nicotine levels is thought to initiate the early stages of withdrawal. How long it takes a smoker to smoke the first cigarette of the day, therefore, serves as a gauge of addiction, with short times indicating stronger addiction. Smoking within 30 minutes of awakening is a key question in the Fagerstrom test for nicotine dependence.²⁸

Several lines of evidence support genetic influences on smoking behavior.^{29–32} Twin studies suggest that genetics accounts for about 50% of the variance in smoking. Interestingly, there appears to be a genetic basis for withdrawal symptoms.³³ A number of genes have been suggested to play a role in both candidate gene and in genome-wide association studies. Although many of the candidate genes have been difficult to reproduce, an extremely strong signal has been consistently observed in a region of chromosome 15 that includes the genes for three nicotinic receptors.³⁴ Among COPD patients, this region is also associated with intensity of smoking assessed by cigarettes smoked per day, suggesting it may be related to intensity of addiction.³⁵ As might be expected of a gene related to smoking behavior, this region has also been strongly linked to the risk for several smoking-related diseases.^{36–39} Candidate genes include not only genes in the dopamine pathway, but also other neurotransmitter pathways as well as cell adhesion molecules that are thought to contribute to long-term memory and neural adaptation.

Genetic variation in nicotine metabolizing enzymes has received particular attention.³¹ Many but not all studies have demonstrated that individuals with variants in CYP2A6 who metabolize nicotine slowly smoke fewer cigarettes and maintain lower cotinine and carbon monoxide levels consistent with their requiring less total intake.^{35,40,41} Consistent with a reduced level of smoking, some studies have shown reduced risk for cancer in slow metabolizers.^{42,43} Similarly, better lung function has been reported among individuals with haplotypes associated with slow metabolism compared to those with genes associated with rapid metabolism who smoke the same number of cigarettes.⁴⁴

It is plausible that the slower decline in blood nicotine levels associated with slow nicotine metabolism makes these individuals less likely to experience withdrawal. In addition, the persistence of

nicotine may decrease the “reward” of smoking. Both of these effects may contribute to increased likelihood that a slow metabolizer can achieve abstinence from smoking,⁴⁰ and better quit rates have been observed among slow metabolizers in clinical trials.^{31,45} On the other hand, slow metabolizers who are experimenting with smoking may have higher and more sustained nicotine levels. Consistent with this, a prospective study of adolescents observed a threefold risk of becoming a regular smoker among slow metabolizers.⁴⁶

Smoking cigarettes is more complex than nicotine addiction. Conditioned behaviors also play a key role.^{1,2} In this context, a smoker typically inhales 10 puffs per cigarette. This would be 300 puffs for a 1.5-pack-per-day smoker or more than 100,000 puffs annually. In addition, smoking frequently occurs in recurrent settings: after eating, when irritated, when bored, when sad, in specific social settings, etc. As such, smoking becomes associated with these settings that serve as operant cues to induce smoking behavior. Nicotine, moreover, has been demonstrated to increase both the intensity of operant conditioning as well as its persistence.^{6,47} The development of addiction to tobacco, therefore, involves not only development of addiction to nicotine, but also acquisition of conditioned behaviors, which nicotine facilitates. Because these cue-mediated behaviors can be very persistent, they are major causes of relapse.

Tobacco addiction most commonly begins in late childhood or adolescence,^{48–51} although smoking can begin in young adulthood.^{52,53} Historically, in the United States, the peak incidence for developing a regular tobacco habit is in adolescence. Individuals who do not acquire a habit prior to age 20 are unlikely to do so as adults.⁴⁸ The demographics of smoking initiation have been well known to the tobacco industry. Marketing campaigns designed to promote the image of specific brands of cigarettes were carefully designed and were exceedingly effective in leading to historic logo recognition among children as young as kindergartners^{51,54} and contributed to brand selection among American adolescents. The susceptibility of children to these campaigns was a major driver in leading to bans on tobacco advertising in media likely to be seen by children. Importantly, since most exploratory smoking occurs in peer-related social settings, the social context of smoking is a crucial variable in determining smoking initiation.^{51,55,56}

Most children who begin to smoke do so on an occasional basis. Within a few years, however, a regular habit may develop. Most often this habit is characterized by smoking only a few cigarettes daily. As noted above, slow metabolizers may be particularly susceptible to addiction due to higher nicotine levels and longer persistence.⁴⁶ The number of cigarettes smoked, however, generally increases for the first 8 to 10 years. Important variations on this pattern exist, suggesting biologic differences among smokers. Some smokers achieve a “mature addiction” very rapidly. In contrast, as many as 15% of smokers, termed “chippers,” may continue to smoke episodically and may not be fully addicted.^{57,58}

Smoking is more common among those with psychiatric disorders.^{59–61} This includes individuals with depression, anxiety disorders, and cognitive disorders such as schizophrenia, as well as other drug dependencies. The basis for this relationship is unclear. Nicotine has modest antidepressant and antianxiety effects, and the suggestion has been made that some individuals with mood disorders may smoke to “auto-medicate.” Alternatively, it has been suggested that smoking and psychiatric disorders may share common genetic risk factors. Another possibility is that smoking early in life may lead to alterations in the CNS that may lead, in turn, to psychiatric disorders. In support of this, smoking more commonly precedes first psychotic episodes.⁶¹ Whatever the mechanisms, the concurrent presence of psychiatric disorders can complicate efforts to achieve smoking abstinence.

Once a smoker achieves a “mature” addiction, cigarette consumption typically remains very constant. Interestingly, the smoker

appears to adjust both nicotine intake and number of cigarettes smoked independently. If supplemental nicotine is administered, smokers will often reduce their cigarette-derived nicotine consumption.⁶² Alternatively, if smoking is restricted, for example, by decreasing the number of cigarettes available, smokers will alter their smoking strategy, for example, by smoking each cigarette more deeply, to maintain a relatively constant nicotine intake.⁶³ Similarly, acidification of the urine increases while alkalinization slows nicotine clearance, and there are corresponding increases and decreases in nicotine intake that are achieved with no change in the number of cigarettes smoked.⁶⁴ Rather, smokers alter the way in which individual cigarettes are smoked, that is, the depth and duration of inhalation and the number of puffs, thus modifying the nicotine absorbed. Consistent with self-regulation of nicotine administration, low-nicotine-content cigarettes do not result in lower nicotine consumption.⁶⁵ This illustrates the complexity of smoking where both nicotine addiction and conditioned behaviors contribute.

While the pathogenetic mechanisms underlying withdrawal symptoms are incompletely understood, it is generally believed that some withdrawal symptoms are related to decreases in nicotine blood levels below certain thresholds. Variations in nicotine metabolism would be expected to affect the timing of symptom onset. Some smokers, for example, may experience nicotine withdrawal at night when sleep interferes with nicotine intake.⁶⁶ The use of nicotine replacement to help ameliorate withdrawal symptoms by maintaining nicotine blood levels is also an important concept underlying nicotine replacement as an aid to smoking cessation. In addition, susceptibility to specific symptoms may be genetically determined.^{67,68}

SMOKING AS A PUBLIC HEALTH PROBLEM

Cigarette smoking is a major public health problem and is, perhaps, the most important cause of preventable disease. The number of deaths attributed to cigarette smoking in the United States has been estimated to be well in excess of 400,000 annually and has been for many years.^{69,70} This exceeds deaths attributed to other specific causes with the recent exception of COVID-19.⁷¹ The health burden attributable to smoking parallels smoking prevalence. As a result, smoking-induced disease is becoming more common in the developing world where smoking prevalence has been increasing, particularly in specific subpopulations such as young and middle-aged males.⁷² In the United States, after comprehensive tobacco control programs were reduced, smoking prevalence and the burden of tobacco-related disease began to decrease.^{73–75} Smoking can cause disease through a variety of mechanisms, which are reviewed in other chapters. However, some pathophysiologic effects persist after cessation. Smoking-related disease, therefore, will continue to be a major health problem for many decades.

Since Dr. Luther Terry released the first Surgeon General's report on smoking and health in 1964,¹⁴ the prevalence of adult smokers in the United States has dropped from 40% to under 14%, although the rate has been relatively stable for the last decade.⁷⁵ Antismoking awareness has increased worldwide to the extent that smoking bans have become commonplace in public buildings, workplaces, and public transportation. In 1984, Surgeon General C. Everett Koop⁷⁶ proclaimed that the United States' number one health goal was to achieve a smoke-free society by the year 2000. Unfortunately, this goal was not achieved, but the public health initiatives that followed had long-lasting effects, evidenced by the continually decreasing overall incidence of smokers in the adult population in the United States.^{73–75} A more realistic goal of adult smoking reduction to 12% in the United States was put into place through the Healthy People 2010 program.⁷⁷ Whether this goal will be obtained remains to be determined; however, it still highlights the importance of a smoke-free society. As of 2020, cigarette smoking reached an all-time low of

13.7% where it has remained.^{76,77} However, this has been associated with a marked increase in vaping among youth (see below). The greatest reductions in smoking have been in states with the most comprehensive tobacco control programs, supporting the effectiveness of currently available interventions.

Public health approaches to control smoking-related disease begin with the social factors that are key in initiating and maintaining smoking.⁵¹ The experience a child has with the initial attempts at smoking appear to be important, as is an individual's attitude toward smoking—that is, the “image” of the smoker, peer pressure, parental cigarette use, and availability.^{51,78,79} Social attitudes can account for very low smoking prevalence in some groups. These observations support attempts to place restrictions on smoking in public places and other efforts to “de-normalize” smoking.⁵¹

As in ancient America, the use of tobacco products has become well integrated into modern cultures worldwide. Tobacco is a multibillion-dollar industry. In some regions, tobacco is a crucial cash crop in an agricultural economy. In addition, the manufacturing, distribution, marketing, and sale of tobacco products employ many individuals worldwide. Taxation on tobacco products has become an important means for the support of many governments. Thus, any changes in tobacco usage are likely to have economic impacts well beyond any health effects.

The use of tobacco has not only an economic role, but a cultural one as well. In some societies—for example, certain Native American tribes—tobacco usage has religious significance. In other groups, tobacco usage is associated with a strong cultural “image.” Often this image may have been created through direct efforts of the tobacco industry to market their product. In this regard, advertising messages promoting the image of the cigarette smoker as rugged, independent, and masculine or as sophisticated, independent, and feminine have been developed.^{80,81} While these images of cigarette smoking have their origins in advertising campaigns, the effectiveness of such marketing programs cannot be underestimated.^{51,79} The portrayal of these images in media, such as film, may help promote smoking, which supports restrictions on advertisements as part of public health initiatives directed at tobacco control.^{51,82,83} Whatever the reasons, cigarettes clearly have a cultural significance. The social and economic impact of tobacco usage, therefore, must be considered when attempting to deal with smoking as a public health problem.

In an effort to combat the public health ramifications of tobacco usage in the United States, the Master Settlement Agreement was signed into effect in 1998.⁸⁴ It served as a measure to recoup what states had lost through Medicaid expenditures due to smoking-related illnesses and as a measure to fine the tobacco industry for deceitful actions. Four major U.S. tobacco companies awarded 46 states \$206 billion to be paid over 25 years and to be utilized as the states saw fit. Four states had previously settled separately. Unfortunately, since its inception, many states have failed to use the funding for tobacco control causes, instead using it to fill budget deficits or to support other state programs. Among many other actions, the agreement also prohibited advertisements targeted at youth and permitted access to tobacco industry documents. Based on current understanding of the complex factors that interact to cause tobacco addiction, these approaches are rational. The issues are also complex and controversial. It is likely that social and public health interventions will continue to evolve and be part of ongoing political debate.

SMOKING PREVENTION

As noted above, smoking initiation is generally a pediatric problem.⁵¹ Precisely why some children begin smoking is not fully understood, although both social and genetic factors contribute as discussed above.⁵¹ Currently, as many as 13.8% of American

children experiment with cigarettes by the twelfth grade.⁸⁵ A number of factors are believed to contribute, including the child's social environment and the child's attitude toward smoking, which appears to be based, in large part, on the smoking behavior of parents, friends, and peer group role models.^{51,78,79} Attitudes toward smoking appear to be important factors leading to smoking initiation, which may depend, at least in part, on advertising and marketing programs, hence the effectiveness of bans on advertising. The reasons for initiating smoking, however, are not entirely environmental, as several lines of investigation (see above) suggest a genetic basis for smoking as well. These concepts support the basis for interventions to reduce smoking initiation. Interventions aimed at altering the social milieu have benefit.⁸⁶ Participation in sporting activities is associated with lower rates of smoking initiation.^{48,87}

A second approach to limiting smoking initiation is to restrict the sale of tobacco products to minors. Many states have legal restrictions on such sales. In many cases, however, these laws are not enforced. Active enforcement, however, can lead to a decrease in sales to minors⁸⁸ and a decrease in both experimental smoking and in regular cigarette use among younger smokers,⁸⁹ although the general effectiveness of these measures is unclear.⁹⁰ For such measures to be effective, they must be uniformly enforced in the community, and vending machines must be made inaccessible to minors.^{91,92} Another approach to restrict tobacco usage by minors is taxation.⁹³ While there is controversy over how "elastic" purchase of tobacco is,⁹⁴ increasing price decreases use, and this effect may be particularly prominent among less addicted smokers.⁹³ Inasmuch as adolescents may have less disposable income, the effect may be even greater among adolescents. Some analyses support an association between higher price, particularly through taxation, and lower smoking initiation and prevalence.⁹⁵ However, assessment of the specific effectiveness is difficult methodologically.

Measures aimed at restricting tobacco sales to minors may lead to a deferral for smoking initiation, as young adults remain at risk for smoking initiation.^{52,53} Thus, if measures are effective at delaying smoking initiation among children, parallel measures may also be required to affect smoking initiation among older adolescents and young adults. Currently available data suggest that smoking behavior among high school students decreased steadily since the initiation of efforts designed to reduce initiation. There does not appear to be a corresponding increase in smoking among older individuals, which supports the concept that smoking prevention is a legitimate and achievable public health goal. While it is difficult to determine the effectiveness of specific public health initiatives,⁹⁶ the evidence is clear that smoking rates can be decreased by population-based measures and that states with the most comprehensive programs have achieved the greatest gains.^{51,73-75}

SMOKING CESSATION

Below we consider a general approach to smoking cessation, patient evaluation, and a variety of nonpharmacologic and pharmacologic approaches to management. We also address practical concerns in a smoking cessation program.

■ Background and General Approach

Smoking should be regarded as a primary addictive disorder.⁹⁷ This contrasts with the "classic" view of smoking as a "habit" or "life style choice." It has been estimated that 75% of American smokers wish to quit but only 3% are able to achieve prolonged abstinence in any year, which indicates the involuntary nature of the established addiction.⁹⁸ In addition, current concepts suggest smoking should be regarded as a chronic relapsing disorder.⁹⁹ In this context, a "cessation attempt" should be regarded as an attempt to induce a remission. The abstinent smoker, moreover, should always be viewed as at

risk for relapse. The goal for therapy is to induce a remission that is as durable as possible. However, the clinician needs to be prepared to re-induce remission in the event that relapse occurs. Smokers who are "quit" should remain in active surveillance, and relapses should not be regarded as "failures." The health consequences of smoking should be regarded as secondary effects. Importantly, there are health benefits of cessation that are well established. These are the subject of the 2014 Surgeon General's Report.¹⁰⁰

Current recommendations are to assess smoking and willingness to quit at every visit.^{97,101} Interestingly, success in quitting may be related to acute problems that may have motivated a patient to be willing to consider quitting (see "Stages of Change and Smoking Cessation," below).¹⁰² This acute motivation may be present even if the acute event is not directly related to smoking, and the clinician should be ready to utilize these windows of opportunity. In contrast, not inquiring about smoking can have adverse effects. Not asking is thought to send three messages: (1) that the physician does not care if the patient smokes; (2) that the physician does not have an effective intervention to offer; and/or (3) that the physician does not think that the patient will be able to quit. All of these "non-messages" have negative effects, particularly as smokers gradually make the decision to quit. A sense of empowerment and control over the behavior is believed to be key to making and succeeding in a quit attempt¹⁰³ and to subsequent risk of relapse.¹⁰⁴ Inadvertently eroding a patient's sense of mastery is an unanticipated adverse consequence of not asking about smoking. In addition, many patients are unaware of the potential available therapies; appropriate information can increase motivation to engage in quit attempts. Smokers unwilling to make a quit attempt should be encouraged as much as possible, provided with specific information if desired, and reminded that the issue will be brought up again in the future.

■ Approach to a Quit Attempt

A smoking quit attempt should be approached in a similar way to induction of remission from cancer. As with cancer, each patient should be given the best chance of achieving remission. In general, this will require two classes of intervention: nonpharmacologic approaches and pharmacotherapy, which should be used together to optimize success.

■ Evaluation

As with the management of any complex disease, smokers should undergo an initial organized assessment.^{97,105} Motivation or reason to quit and the patient's confidence in their ability to stop smoking, that is, self-efficacy, should be assessed. For patients who indicate they are not currently interested in quitting, the goal is simple: to move them through the stages of change¹⁰⁶ so a quit attempt will be made. For some, this may be as simple as providing information about health risks. For others, it may be information about effective interventions. Motivational Interviewing is an effective technique used to guide patients toward change.¹⁰⁷ It allows patients to discover their own internal motivation through a nonjudgmental process of exploration. The provider provides empathy, rolls with resistance, respects patient autonomy, and empowers the patient to make changes on their own terms and at their own pace.

The intensity of addiction can be assessed with the Fagerstrom test for nicotine dependence (Table 41-1).²⁸ The most important question is time to first cigarette, and smokers who smoke within 30 minutes of awakening are usually heavily addicted to nicotine. These patients and those with Fagerstrom scores ≥ 7 constitute a group of individuals likely to benefit from nicotine replacement therapy (NRT) and varenicline and more efficacious as monotherapy as compared with bupropion. In contrast, patients with low Fagerstrom scores who are able to cope with smoke-free environments for an extended time period (>4 hours) without developing

TABLE 41-1 Items and Scoring for Fagerstrom Test for Nicotine Dependence

| Questions | Answers | Points |
|--|------------------------------|--------|
| 1. How soon after you wake up do you smoke your first cigarette? | Within 5 min | 3 |
| | 6–30 min | 2 |
| | 31–60 min | 1 |
| | After 60 min | 0 |
| 2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in cinema, etc.? | Yes | 1 |
| | No | 0 |
| 3. Which cigarette would you hate most to give up? | The first one in the morning | 1 |
| | All others | 0 |
| 4. How many cigarettes/day do you smoke? | 10 or less | 0 |
| | 11–20 | 1 |
| | 21–30 | 2 |
| | 31 or more | 3 |
| 5. Do you smoke more frequently during the first hours after waking than during the rest of the day? | Yes | 1 |
| | No | 0 |
| 6. Do you smoke if you are so ill that you are in bed most of the day? | Yes | 1 |
| | No | 0 |

Reproduced with permission from K.O. Fagerstrom.

discomforting withdrawal symptoms may not require NRT. For these individuals, the benefit of pharmacologic support is unknown.

Past experience with quit attempts should be reviewed. Many patients will have a number of prior tries. Individuals who had particular difficulty with withdrawal symptoms should be prepared for this, and medications can be gauged to attempt to mitigate their intensity. Approaches that achieved abstinence, but were followed by relapse, should be considered as they are likely to succeed again. In these cases, interventions should be guided by reducing risks of relapse.

■ Nonpharmacologic Approaches

Nonpharmacologic approaches provide the smoker with guidance and support as progress is made through a quit attempt.^{97,105} It is likely that effective support improves adherence with pharmacotherapy and results in therapeutic synergy. In addition, conditioned responses, that is, cue-driven behaviors, are largely dealt with thorough behavioral strategies. This generally requires individual interviews to define individual smoking patterns. These patterns can also help identify situations that increase risk of relapse. In general, success increases with the intensity of support, but most smokers will decline referral to intensive programs and will receive only the support provided in the office setting. The remainder of this section summarizes commonly used approaches.^{97,105,108}

Stages of Change and Smoking Cessation

The Stages of Change model has been very useful to guide behavioral support. Prochaska and DiClemente¹⁰⁶ described the smoking cessation process as involving five stages: precontemplation, contemplation, preparation, action, and maintenance. These stages are viewed as a continuum with smokers progressing sequentially through each stage. In the precontemplation stage, smokers are not interested in quitting smoking and will likely be nonresponsive to direct intervention. Smokers in the contemplation stage are

considering quitting smoking and may be receptive to a physician's advice about the risks and benefits of quitting. In the preparation stage, smokers are actively preparing to quit. The action stage encompasses both initial abstinence and the 6-month post-cessation period. The maintenance period commences after the 6-month abstinence period. It is rare for a smoker to progress successfully through these stages in the initial quit attempt. The cycle will likely be repeated several times before smoking a prolonged abstinence, that is remission, is achieved. Thus, the clinician must be encouraging and willing to support repeated attempts.

The National Cancer Institute's (NCI) recommended model for smoking intervention is based, in part, on five NCI-supported trials involving more than 30,000 patients and was later expanded by the Public Health Service.^{97,105} This approach, popularly referred to as "the five A's," emphasizes the role of medical professionals to ask patients about their smoking status, assess their willingness to make a quit attempt, advise smokers to stop, assist them in their stop smoking efforts, and arrange for follow-up visits to support the patient's efforts. This approach utilizes brief intervention techniques and emphasizes the role of physicians as facilitators in the quitting process.

Simple advice has been assessed in a number of studies, and meta-analysis suggests a small but significant benefit of these limited interventions.^{97,105} Physician advice is effective both in the outpatient and hospital setting and may also be effective when given by letter, email, or telephone.^{109–111}

Group Counseling

Group counseling programs for smoking cessation are offered by several commercial and voluntary health organizations. These programs are similar in content and typically include lectures, group interactions, exercises on self-recognition of one's habit, some form of tapering method leading to a quit day, development of coping skills, and suggestions for relapse prevention. Group counseling programs sponsored by voluntary health organizations are generally the best cost value for smokers. However, these programs are generally limited to large metropolitan areas and are offered on a sporadic basis. One-year success rates associated with group counseling programs are typically in the 15% to 35% range.^{97,105} The high success rates are likely affected by selection bias, that is, participants may be more motivated to quit.

Gradual Reduction Versus Abrupt Abstinence

It is unclear whether gradual reduction in cigarettes smoked per day or abrupt abstinence is the better method for achieving prolonged smoking cessation; results may depend on individual factors.

The optimal approach probably requires customization to the patient's specific needs. Gradual reduction or tapering intuitively appears to offer smokers the least abrasive way to stop smoking and may be effective for some.^{112–114} However, gradually cutting down can be stressful when smokers attempt to reduce their cigarette use below their critical blood nicotine threshold. At this stage, smokers may begin to experience tobacco withdrawal symptoms. Rather than suffer prolonged discomfort, many taperers will gradually return to their customary cigarette levels and will not succeed in quitting. One of the negative consequences of tapering is that this method can strongly reinforce the smoker's belief of their underlying need for cigarettes; that is, it can undermine self-efficacy. Combining tapering with pharmacotherapy to prevent withdrawal may be useful in this setting.¹¹³ In this context, gradual reduction with varenicline is included in package label. Abrupt abstinence is often stressful and can lead to tobacco withdrawal symptoms. However, within a few weeks of total abstinence, complete abstainers experience less frequent cigarette cravings than taperers and are less prone to relapse. Cigarette tapering is often a component of

many group programs in which gradual cigarette reduction is used as a preparatory stage leading toward a target quit day.

Educational Techniques

For years, cigarette smoking was viewed as largely a social or psychological habit. As such, the ability to quit was viewed as a measure of personal motivation and psychological willpower. Motivation to stop smoking, combined with sufficient psychological resources, was seen as a driving force behind successful cigarette abstinence. Thus, if smokers could be educated about the health risks of cigarette smoking, they could theoretically become sufficiently motivated and psychologically empowered to quit. Unfortunately, anticipated benefits of the smoking cessation value of educational awareness messages were overly optimistic and simplistic. Educational programs to aid smoking cessation have produced disappointing results with high long-term failure rates.^{97,105} Nevertheless, education about smoking is still regarded as a useful activity, particularly when the information can address problems of specific interest to individual patients. In this regard, as noted above, a major predictor of success is “self-efficacy,” which is the patient’s sense that they are likely to succeed. Education that improves self-efficacy should be a therapeutic goal.

Other Modes of Smoking Cessation

The goal of hypnosis in smoking cessation is to enable the smoker to achieve an altered state of consciousness to enhance the ability to quit. Controlled trials of hypnosis have generally been unable to document long-term smoking cessation efficacy. While one meta-analysis suggested the possibility of a treatment effect,¹¹⁵ this was not supported in another meta-analysis.¹¹⁶ Aversive conditioning is based on the premise that smoking is a learned response that can be extinguished by creating an association between smoking and a negative sensation. By design, aversive conditioning techniques can produce smoker discomfort and are now rarely employed. However, there are few recent studies, and a treatment benefit cannot be excluded.¹¹⁵ Acupuncture has been advocated, but controlled trials with “sham” acupuncture have not clearly demonstrated an effect. Meta-analyses have not been conclusive but suggest the possibility of an effect.¹¹⁵

Available Resources

The resources available to support smoking cessation vary among communities. Some have readily available and affordable group programs, while these may be unavailable in other places. Toll-free tobacco quit lines are currently provided by many countries, including the United States and Canada. Telephone counseling is an effective smoking intervention.¹¹¹ Thus, clinicians should encourage every smoker who wishes to quit to utilize a National Quit Line (e.g., in the United States: 1-800-Quit-Now). Additional support can be found via the internet using smokefree.gov. Using this approach, a smoker can choose to talk with a telephone specialist with either internet instant messaging or telephone support. Both methods are designed to provide smokers with a personalized quit plan that would be available in most clinical settings.

■ Pharmacologic Treatment

Three classes of agents, nicotine replacement, bupropion, and varenicline, are approved to aid smoking cessation.¹¹⁷ In addition, two other agents, clonidine and nortriptyline, are supported by guidelines for “off-label” use as secondary agents. In addition, several other agents are under active investigation and have shown promise.^{97,105,117} As noted above, combination of nonpharmacologic support and pharmacotherapy optimizes success in achieving abstinence. The remainder of this section summarizes currently available pharmacotherapy.

Nicotine Replacement Therapies

Five nicotine replacement therapies are approved for use to aid in smoking cessation. Lozenges, polacrilex (gum), and transdermal systems are available over the counter (OTC). Nasal spray and a nicotine inhaler are available with a prescription. Initial concerns about potential hazards of concurrent smoking while using NRT led to warnings against this practice. However, the U.S. Food and Drug Administration (FDA) removed this warning from the OTC formulations, as the benefits of smoking cessation greatly exceed any potential hazards.

NRT is usually started on the scheduled quit day. The concept is to replace nicotine that would be absorbed from cigarettes and thereby reduce the intensity of withdrawal. Smokers will, however, experience withdrawal symptoms—albeit with less intensity. In clinical trials, the five approved formulations have demonstrated about twofold increases in quit rates above placebo when used alone,^{97,105} and one trial comparing gum, inhaler, and nasal spray found no difference in efficacy.¹¹⁸ They differ, however, in their pharmacokinetics.¹¹⁹ Transdermal systems provide the slowest delivery of nicotine but maintain steady-state levels throughout the day. The other formulations allow episodic dosing. A common practice is to combine a transdermal system with another formulation, a “patch-plus” regimen.^{120,121} This allows a smoker to increase nicotine delivery at times of urges. Clinical trial data support better success with combined NRT compared to monotherapy.^{97,105}

Nicotine Polacrilex Gum Nicotine polacrilex gum was the first NRT to gain FDA approval. It is now commercially available OTC in 2- and 4-mg forms. In nicotine polacrilex, nicotine is bound to a resin that contains a buffering agent to improve delivery of nicotine through the buccal mucosa. The rate of chewing can influence the rate of nicotine release. In addition, acid foods or drinks convert nicotine base to its salt, which, because of its charge, does not cross the buccal mucosa. To be absorbed into the venous circulation, the nicotine-containing saliva must be retained in the mouth as long as possible. If swallowed, the nicotine can cause local irritation of the stomach. When absorbed into the portal circulation, high first-pass metabolism in the liver limits blood nicotine levels. If chewed properly, absorption takes place gradually, and blood levels peak after about 30 minutes.¹¹⁹ Ad lib use of 2-mg nicotine polacrilex is associated with blood nicotine levels less than 40% of customary smoking. The 4-mg dose is recommended for individuals who are heavier smokers or who have had discomforting tobacco withdrawal symptoms on the 2-mg dose.^{97,105} A fixed dosage regimen, rather than ad lib usage, may have better success,¹²² perhaps because it can produce higher blood nicotine levels. A common recommendation is that a smoker use one piece of gum every 1 to 2 h for the first 6 weeks after quitting followed by gradual reduction over 6 weeks. Many smokers continue to use gum at times of craving for an extended time, and some can use sufficient gum to sustain nicotine addiction without smoking.

Although effective in clinical trials, less successful results have been observed with nicotine gum in general practice and unsupervised settings. This may be due, in part, to requirement that the gum be chewed properly. Adverse effects from the gum include exacerbation of local effects: temporomandibular joint (TMJ) disease, trauma to dental appliances, sore jaw, oral irritation or ulcers, and excess salivation; effects from swallowed nicotine: hiccups; and effects from systemic absorption of nicotine: nausea, vomiting, abdominal pain, constipation, diarrhea, palpitations, and headache. Use of the gum is not recommended in individuals with poor dentition or who have dental appliances.¹¹⁷

Nicotine Polacrilex Lozenge A nicotine polacrilex lozenge is also available “over the counter.” Chewing is not required, but acid food and/or beverages will impair absorption as with gum. Dosing,

absorption, and duration of therapy with the lozenge are similar to those for the gum.¹²³ Because it is not chewed, the lozenge does not share the problems of exacerbating TMJ disease or damaging dental appliances. Other side effects are similar to those of the gum.

Transdermal Nicotine The primary advantage of transdermal patch delivery systems are ease of use and controlled drug delivery. Several formulations are available “over the counter.” In general, they achieve nicotine blood levels roughly 40% to 50% of that achieved by customary smoking of about 30 cigarettes daily.¹¹⁷ Transdermal nicotine systems have been repeatedly found to reduce tobacco withdrawal symptoms and significantly enhance smoking cessation rates.^{97,105} Unlike nicotine polacrilex gum, transdermal nicotine systems and the nicotine lozenge have improved quit rates in primary care settings.^{102,124} This difference is likely due to the ease of patch use in this setting. The recommended use period for patches varies according to product, but a minimum of 4 weeks of therapy is probably required to help achieve long-term abstinence. Long-term patch use is safe and likely beneficial for many smokers.¹²⁵

Patches are most commonly worn at night, providing a level of nicotine when a smoker awakes. Often this is a time when the individual is at risk to relapse, since the low nicotine levels are associated both with withdrawal and with increased effect of the smoked cigarette. On the other hand, delivery of nicotine at night may disturb sleep, particularly through vivid dreams or insomnia. Spontaneous long-term use of the patch has not been observed, suggesting that the very slow kinetics of nicotine delivery with this system is insufficient to sustain addiction effectively.¹²⁶ In addition, perhaps due to the partial replacement of nicotine, most smokers on patches will still experience some tobacco withdrawal symptoms during the first few days of quitting. While these symptoms will likely be less severe compared to quitting cold turkey, some patients will be tempted to smoke and wear patches. Early concerns about increased cardiac risk among individuals who smoked while wearing the patch have not been substantiated. In fact, reduced smoking may decrease cardiac events.¹²⁷

Nicotine Inhaler The nicotine inhaler is a plastic nicotine-containing cartridge that fits on a mouthpiece. Nicotine is released when air is inhaled through the device, which is similar in size to a cigarette. The nicotine is not effectively delivered to the lungs as the particle size is too large. Rather, it is deposited and absorbed through the buccal mucosa, which results in pharmacokinetics that resemble nicotine polacrilex. Blood levels depend on the frequency of inhalations but can be about one-third of conventional smoking. Usual dosing is 6 to 16 cartridges per day for 6 to 12 weeks followed by gradual reduction over 6 to 12 weeks. Because the use of the inhaler recapitulates many of the actions associated with smoking such as the preparation of the device, oral stimulation, inhalation, and others, the inhalers may be particularly effective in smokers for whom these behaviors are particularly strongly conditioned. In addition to the adverse effects described for the lozenge, the inhaler may cause irritation of the throat and mouth and may precipitate bronchospasm in individuals with reactive airways.

Nicotine Nasal Spray The nasal spray delivers nicotine to the nasal mucosa through which it is absorbed. It has the most rapid pharmacokinetics of the currently available nicotine replacement formulations but does not reproduce that of a cigarette.¹¹⁹ Nasal irritation is very common, particularly when initiating therapy. The recommended dose is one to two sprays per hour for 3 months with a maximum of 80 sprays per day. Because the spray can deliver large amounts of nicotine, it may be particularly effective for heavily addicted smokers. It also likely has a greater risk of nicotine overdose and may have a greater potential to sustain a long-term addiction.

Combination Therapy Various combinations of nicotine replacement may have utility for selected individuals who need higher

doses. In particular, combination of a transdermal system with an ad lib modality has been demonstrated to increase quit rates.^{97,105,124,128} Because of its increased success, it is recommended by some as initial therapy.¹¹⁷

Bupropion Bupropion is approved as an antidepressant, and it is also effective as an aid for smoking cessation.^{97,105,129} It is believed to act by potentiating dopaminergic and noradrenergic signaling. The formulations for depression and for smoking cessation have different trade names and dosages, which has clinical relevance. First, an appropriate diagnosis is often required for reimbursement. Second, care is needed not to prescribe bupropion under one name to an individual already taking it under its other name, as overdosage can result.

In clinical trials, bupropion approximately doubles quit rates compared to placebo. Subjects with a history of depression, however, appeared to benefit from bupropion but did not with nicotine replacement, suggesting that bupropion may be a superior initial choice in such individuals. Combination of nicotine replacement with bupropion has been assessed and appears more effective than either agent alone.

The currently recommended dose is 150 mg daily for 3 days, followed by 150 mg twice daily. Because the drug is excreted slowly, steady state-levels are achieved after 6 to 7 days. For this reason, the quit date should be scheduled after a week of therapy so that blood levels are established. As the 150-mg once-daily dose was nearly as effective as the 150-mg twice-daily,^{130,131} many practitioners use the lower dose routinely. The appropriate duration of therapy is not established. Clinical trials that formed the basis for approval treated for 7 weeks, although a 12-week course is commonly recommended. With prolonged therapy, there is an increase in secondary quits, and therapy for 1 year resulted in more quits than therapy for 7 weeks.

The drug is generally well tolerated. The most common adverse effects are dry mouth, insomnia, agitation, and headache. In combination with nicotine replacement, an increase in blood pressure also may occur. Bupropion reduces seizure threshold, and a seizure risk of 0.1% has been reported. Because of its reduction in seizure threshold, bupropion is contraindicated among those predisposed to seizures, or with anorexia nervosa or bulimia.

In 2008, the FDA first noted that both bupropion and varenicline (see below) had a “possible association (with) suicidal events.”¹³² The benefits of smoking cessation were felt to outweigh any potential risks, and the medicines were not withdrawn from the market. In 2016, the FDA removed the black box warning about possible suicidal events from the labels of both bupropion and varenicline following a subsequent large randomized controlled trial showing that the rates of major adverse psychiatric events were similar across all tobacco treatments (including varenicline, bupropion, and NRT) compared with placebo.¹³³ The rate of adverse psychiatric events was about 6% in patients with underlying psychiatric illness and 2% in otherwise healthy individuals. Thus, regardless of the treatment strategy chosen, it is important for all patients and their caregivers to monitor for possibility of neuropsychiatric symptoms, and patients should be monitored for changes in behavior, hostility, agitation, depressed mood, suicidal ideation, and suicide attempts. Most practitioners make a routine practice of reassessing patients 3 to 7 days after the quit day to both monitor for adverse effects and to provide additional support for the quit attempt. In this context, a second visit has been demonstrated to greatly improve success.^{97,105,117}

Varenicline Varenicline is a partial agonist at the $\alpha 4\beta 2$ nicotinic receptor.¹³⁴ As such, it can partially activate the receptor thereby mitigating withdrawal symptoms. In addition, by occupying the receptor, it can prevent nicotine from acting, and thus can reduce the rewarding and reinforcement effects associated with nicotine. This may be particularly important in preventing a lapse from becoming

a full relapse once abstinence has been achieved. Both of these effects are supported by evidence from clinical trials.^{135–138} Varenicline consistently improves success in quitting compared to placebo by an effect of two- to fourfold.¹³⁸ In addition, head-to-head trials have demonstrated superiority compared to bupropion,^{133,135,136} as well as to nicotine replacement.¹³³

Varenicline is given orally. Usually medicine is started at 0.5 mg once daily for 3 days followed by 0.5 mg twice daily for 4 days and then 1 mg twice daily for 3 months. Individuals who have achieved abstinence at 3 months may have less relapse if therapy is continued for an additional 3 months. A quit date is usually recommended for 1 week after starting medication, but success has been reported with a broader window of quit dates from 1 to 5 weeks that was comparable to a fixed quit rate.^{139,140} Gradual scheduled reduction may be helpful during this extended period. This increased flexibility may be an advantage in starting a quit attempt when patients are seen for problems other than smoking cessation.

The most common adverse reactions are nausea, insomnia, visual disturbances, syncope, and skin reactions. The incidence of nausea is reduced with the dose titration described above.¹⁴¹ The most serious concerns with varenicline have been with psychiatric and cardiovascular side effects. Varenicline had the same boxed warning as bupropion, indicating that patients and their caregivers should be alerted to the possibility of neuropsychiatric symptoms, which, as noted above, has been removed.¹³² Consistently, clinical trials have failed to confirm psychiatric adverse effects.¹⁴² A meta-analysis that reported significant increase in cardiovascular events¹⁴³ was felt to be methodologically flawed, as it excluded studies with no events.¹⁴⁴ A subsequent meta-analysis that included all available studies found no difference between varenicline and placebo, although a small difference may be present.¹⁴⁴ Based on this information FDA recommended that patients taking varenicline be alert for development of new or worsening symptoms of cardiovascular disease.¹⁴⁵ Varenicline has also been associated with accidental injuries from falls and vehicular accidents.¹⁴⁶ This has resulted in an FDA advisory regarding operating heavy machinery while using varenicline.¹⁴⁷

Off-Label Agents

A number of drugs have been used “off-label” in smoking cessation programs. Two are briefly considered below.

Clonidine Clonidine is an α-adrenergic agonist active in the CNS that is used to treat hypertension. A number of clinical trials have evaluated its efficacy in smoking cessation and have generally shown a trend toward benefit, although individual trials have generally not been statistically significant, and its use is supported by a meta-analysis.¹⁴⁸ The Department of Health and Human Services (DHHS) guidelines have suggested it can be used by experienced practitioners comfortable with the drug.^{97,105} Major adverse effects of clonidine are drowsiness, fatigue, dry mouth, and postural hypotension.

Nortriptyline Nortriptyline is a tricyclic antidepressant that has been evaluated for efficacy in smoking cessation in several studies. Both individual studies and meta-analyses support its benefit as an aid to smoking cessation,^{129,149} and it has also been recommended as a possible second-line agent for practitioners comfortable with its use by the DHHS guidelines.^{97,105} Major adverse effects of nortriptyline include drowsiness and dry mouth. As with other tricyclics, CNS and cardiovascular effects, including arrhythmias, may occur.

■ Practical Concerns During the Quit Attempt

Smoking cessation entails consideration of a variety of practical concerns, including the general approach to be employed, patient withdrawal symptoms, including cravings and depression, and weight gain, as discussed below.

Approach

As noted above, the first step is to have a patient willing to make a quit attempt. Current practice is to optimize the chance for success with each attempt. In general, this will be achieved with nonpharmacologic support combined with pharmacotherapy. The more active the nonpharmacologic support the greater the likelihood of success. Patients vary, however, in the type of support they will accept.

It is also important to select an appropriate pharmacotherapy. The initial choice is typically customized and depends on several factors including the patient's prior experience, comorbidities, preferences, and cost. Many practitioners initiate treatment with NRT, because of greater experience and reduced potential for adverse effects. The “patch-plus” regimen that combines a transdermal system with an ad lib formulation is often recommended.^{97,105,117} Bupropion may be more appropriate for individuals with a history of depression.¹³⁶ Varenicline has the greatest efficacy.¹¹⁷ The quit date should be linked to the pharmacotherapy: generally, this is 1 week after initiating bupropion or varenicline and on the same day as initiating NRT. Varenicline may offer some flexibility, with a quit date 1 to 5 weeks after starting treatment.¹⁴⁰ A follow-up visit should be scheduled about 10 days after initiating therapy to check for side effects, withdrawal symptoms, and general treatment effectiveness. A follow-up in the immediate post-quitting period is associated with improved success. This may be particularly important for cessation attempts that begin in hospital.¹⁵⁰ Longitudinal follow-up for this chronic relapsing/remitting condition is important.

Withdrawal Symptoms

The first 3 days of abstinence are usually the most difficult. Tobacco withdrawal symptoms (Table 41-2) generally peak during the first 72 hours and then gradually subside over a 3- to 4-week period. These symptoms can include restlessness, anxiety, difficulty concentrating, irritability, frustration, depression, and an almost unrelenting craving for cigarettes. Common suggestions to help smokers cope with these early withdrawal symptoms in addition to NRT can include: (1) Be active. Increased activity may curtail some of the drive to smoke. (2) Use deep breathing exercises. The simplest breathing exercise involves nothing more than extended breath holding followed by slow exhalation through pursed lips. (3) Avoid high-risk situations for smoking during the first 3 weeks of quitting. (4) Use plenty of cinnamon gum or chewable candies. (5) Combat strong urges to smoke: The urge to smoke will go away whether one smokes or not.

Cravings Of all the symptoms associated with nicotine withdrawal, cravings to smoke are the most persistent. Unlike the other symptoms, cravings can also recur long after abstinence is achieved. During the second and third weeks of abstinence, the craving waves

TABLE 41-2 Nicotine Withdrawal Symptoms (DSM-IV)

| |
|-------------------------------------|
| Dysphoric or depressed mood |
| Insomnia |
| Irritability, frustration, or anger |
| Anxiety |
| Difficulty concentrating |
| Restlessness |
| Decreased heart rate |
| Increased appetite or weight gain |

usually occur less frequently, but can sometimes catch smokers off guard because of their unexpected intensity. The decrease in frequency is greater than the decrease in intensity, and cravings can be precipitated months and years after abstinence if precipitated by specific cues. In this context, cravings recapitulate, in some ways, the grief response. Relapse is commonly associated with concurrent alcohol consumption. It is likely that alcohol, and the associated situations in which it is consumed, serves both as a cue leading to craving and decreases the inhibitions that may prevent smoking. Ex-smokers should be aware of these moments of hazard.

Depression At some time during the first 3 months of abstinence, some smokers may experience depression. For many this depression is mild and transient. For a small minority of smokers, quitting smoking may produce a clinical depression that may require anti-depressant therapy, counseling, or return to smoking. Depressive symptoms are associated with relapse.¹⁵¹

Weight Gain

One of the most disheartening components of quitting smoking is weight gain.^{97,105} Rapid weight gain is common during the first 6 to 8 weeks of cigarette abstinence. This is followed by a more gradual increase in weight to roughly 4 kg at 6 months. Average weight gain at 10 years following cessation is 4.4 kg and 5.0 kg for males and females, respectively. The health risks associated with post-cessation weight gain are unknown but are likely surpassed by the health benefits of stopping smoking.

RISKS OF SMOKING CESSATION

Smoking cessation may be associated with some hazards in selected cases. Nicotine and other components of cigarette smoke may have a significant antidepressant effect, and many endogenously depressed individuals may have empirically found smoking helped alleviate their symptoms. Depression is a well-recognized manifestation of the nicotine withdrawal syndrome. At times, this depression can be of major clinical importance. Exacerbations of ulcerative colitis are more common in former smokers and may develop at times long after smoking cessation.¹⁵² These potential adverse effects should not minimize the importance of smoking cessation, but the clinician should be prepared to address them when necessary. Anecdotal reports have suggested that asthma may worsen following cessation. However, smoking generally makes asthmatics worse¹⁵³ and induces resistance to the therapeutic effects of inhaled glucocorticoids. Thus, asthma symptoms generally improve with smoking cessation.¹⁵⁴ Some smokers report an increase in cough in the weeks following cessation. However, among individuals with chronic bronchitis, symptoms of cough and sputum production decrease dramatically in the months following cessation.^{155,156}

SPECIAL POPULATIONS

Smoking cessation approaches for special populations (e.g., hospitalized patients, those with medical and psychiatric comorbidities, and pregnant patients) are generally the same as for the general population.¹⁵⁷ Smoking cessation treatment can be started in hospital at the time of acute illness.¹⁵³ Success depends on adequate follow-up and support. Interestingly, withdrawal symptoms may be particularly mild in hospital, perhaps because there are few options to smoke. Concurrent treatment of individuals hospitalized with psychiatric illness for smoking cessation can be successful and does not compromise treatment of the comorbid psychiatric problem.¹⁵⁷ Treatment of pregnant smokers has been extensively reviewed.¹⁵⁸

Smoking is a major risk factor for COPD. All three approved forms of pharmacotherapy, NRT,¹⁵⁹ bupropion,¹⁶⁰ and varenicline,¹⁶¹ have demonstrated efficacy in the COPD population.

HARM REDUCTION

A more controversial approach for smokers who are unwilling or unable to quit at all, is that the health consequences may be partially addressed by reducing the exposure to smoke-derived toxins. This approach, termed "harm reduction," has been the subject of several reviews, including an Institute of Medicine report.^{162,163} Four general categories of harm reduction are theoretically possible: (1) administration of agents to counteract the effects of cigarette smoking; (2) smoking reduction; (3) development of less toxic tobacco products; and (4) alternate nicotine delivery systems. This has become particularly important with the rapid increase in prevalence of vaping (see below). It is important to recognize that clear health benefits have not been established for any of these approaches, however, and novel health risks have been clearly associated with vaping.

Since cigarette smoking is thought to cause its effects through pathogenetic mechanisms that are at least partially defined, it is appealing to use such mechanisms as targets for therapeutic intervention. In this regard, antioxidants to ameliorate the oxidant-induced injury caused by cigarette smoke, and protease inhibitors to bolster the antiprotease defenses, are both potential therapies. While conceptually appealing, no data exist to suggest that any such approach is of benefit in continuing smokers.

Pharmacologic support may facilitate reduction in smoking. The observation that most smokers maintain a relatively constant nicotine intake creates the possibility that nicotine replacement can help sustain smoking reduction. Smoking reduction has also been achieved with several formulations of nicotine replacement, and there is some evidence for physiologic benefit. Short-term smoking reduction, facilitated with the use of nicotine polacrilex gum, was associated with improvements in lower respiratory tract inflammation assessed by bronchoscopy and bronchoalveolar lavage in a group of heavy smokers.^{164,165} In patients with cardiac disease who reduced smoking, there were measurable improvements in cardiac function that were associated with improved oxygen delivery to the heart due to reduced carbon monoxide.¹⁶⁶

Reducing the delivery of cigarette smoke toxins while still providing the smoker with a satisfactory cigarette has been pursued by some tobacco companies. This was a major motivation in the development of filtered cigarettes and of low-tar, low-nicotine cigarettes. Unfortunately, these approaches do not reduce, and may actually increase, exposure to smoke-derived toxins. As most smokers maintain constant nicotine intake, many smokers compensate for altered smoke composition by simply smoking more or by changing the way in which they smoke each cigarette.^{167,168} By causing an altered smoking strategy, filtered and low-yield cigarettes may actually deliver more toxins.

Many of the cigarette-derived toxins are generated as a result of pyrolysis.²⁵ As a result, tobacco products that do not burn have the promise to yield fewer toxins. Several cigarette-like devices have been developed with similar goals. Some burn small amounts of processed tobacco together with a carbon heat source to have a taste that more closely resembles a cigarette.¹⁶⁹ Others electrically heat the tobacco. Whether the electronic cigarette will be effective as an alternative to smoking at present remains to be determined (described in more detail below).¹⁶³ Because of the rapid and widespread uptake, electronic cigarettes ("e-cigs" or vaping) have been particularly controversial and are discussed in detail in the following section. This led to early reviews and position statements by medical groups including the pulmonary community relating to these products.^{170,171} Potential harm-reduction products appear to deliver less toxins in standardized smoking regimes. However, limited data are available on physiologic effects. In one study, a reduction in lower respiratory tract inflammation and airway metaplasia was observed among heavy smokers who switched to a harm-reduction product.¹⁷² Whether such products are associated with health benefits, however, remains to be determined.

Non-burned tobacco products may also have advantages. Moist snuff, which has low nitrosamine content due to its processing, has been widely used for several decades in Sweden. It has been associated with a measurable decrease in a number of tobacco-related diseases among Swedish men compared with cigarettes, but not compared with abstinence.^{173–176}

Harm-reduction strategies may have unforeseen problems. Reduced-risk products or smoking reduction strategies may encourage smokers to continue and thus discourage quit attempts. Available data, however, suggest the opposite. Smokers who switch to harm-reduction products or who reduce with pharmacologic support appear to have an increased rate of subsequent quits. It may be that the sense of mastery that comes with the reduction effort helps make smokers “able” to quit. There are other potential hazards. Reduced-risk products, for example, might be particularly appealing for individuals beginning smoking both because they may be easier to smoke and because they are not perceived as having significant risks. Finally, if use of reduced-risk products erodes the social climate that discourages smoking, such products could increase use of conventional cigarettes.

ELECTRONIC CIGARETTES AND VAPING

Electronic cigarettes (EC, also known as “electronic nicotine delivery systems”) are battery-operated devices that heat and aerosolize a liquid solution (an “e-liquid”).¹⁷⁷ E-liquids typically, but not always, contain nicotine. The other main e-liquid components include alcohol-based solvents (propylene glycol and vegetable glycerin) and flavorings.¹⁷⁸ Upon heating, this solution becomes more complex and releases toxic constituents (aldehydes, acrolein), though in much lower quantities compared with combustible cigarettes.¹⁷⁹ The commercialization of ECs developed independently of big tobacco companies,¹⁸⁰ and the products were initially conceived as a harm reduction tool for cigarette smokers.¹⁸¹ Over time, however, ECs have provoked substantial controversy among tobacco control experts.¹⁸² On one hand, individuals switching completely from cigarettes to ECs might substantially reduce exposure to combustion products and other toxicants.¹⁸³ On the other, the products may expose youth and nonsmokers to potent nicotine products that could engender addiction and cause additional health risks.^{184,185}

ECs contain three basic components: (1) a battery to provide heat; (2) a metal heating element; and (3) a liquid solution.¹⁷⁷ Within this basic structure, ECs are highly heterogeneous with respect to product design, emissions, toxicity, and nicotine delivery.^{186,187} They vary by size, strength of battery, accessibility by the user (i.e., open or closed systems), and the e-liquid used (resulting in countless combinations of nicotine concentration and flavorings).

EC use is known as “vaping.” Vaping is the inhalation of a heated, aerosolized substance. It is distinguished from smoking by its lower temperature and the absence of combustion products in the inhaled aerosol. Although ECs were initially designed for vaping nicotine, it has become recognized more recently that some people use EC devices to consume other substances such as tetrahydrocannabinol (THC), the main psychoactive chemical in marijuana.¹⁸⁸ The implications of these new EC use patterns may have a significant health impact (see “E-Cigarette or Vaping Product Use–Associated Lung Injury,” below).

■ Electronic Cigarettes and Public Health

The net effect of ECs on public health remains a subject of heated debate and is currently unknown. Since its inception, EC use has skyrocketed among youth and young adults, while use of combustible cigarettes has dropped steadily to an all-time low.¹⁸⁹ The long-term implications of this trend raise significant questions and concerns. Does long-term use of ECs produce similar health harms

compared with cigarette smoking? Will the uptake of ECs lead to more or fewer combustible cigarette smokers in the future? Will a new generation of young people develop addiction to nicotine?

A comprehensive scientific review of ECs was published in 2018 by the National Academy of Sciences.¹⁷⁷ The data to date provide conclusive evidence that most EC products emit toxic substances, that EC toxicity varies substantially among products and individual use patterns, that accidental high-dose exposure to e-liquids or faulty EC batteries can be highly hazardous, and that completely substituting ECs for regular cigarettes reduces user exposure to many toxicants and carcinogens.¹⁷⁷ Substantial evidence suggests: (1) that nicotine exposure from ECs can induce dependence and may be similar to combustible cigarettes in some users, (2) that exposure to toxic substances is significantly lower compared with combustible cigarettes, (3) that EC aerosol constituents can induce endothelial dysfunction, oxidative stress, and DNA damage, (4) that youth who use ECs may be at higher risk of subsequent combustible cigarette smoking, and (5) that completely switching to ECs from combustible cigarettes may reduce short-term adverse health outcomes in several organ systems.

Despite the existing evidence, many key questions remain unanswered. Do ECs lead to pulmonary, cardiovascular, and oncologic diseases? If so, how does disease onset, probability, and severity compare with chronic cigarette smoking? Will the presence of ECs ultimately reduce or increase combustible cigarette use at the population level? How addictive are ECs compared with combustible cigarettes? What will this mean for public health? These questions will need to be answered over the next several decades through careful investigation.

■ Electronic Cigarettes in Smoking Cessation and Tobacco Harm Reduction

The overwhelming majority of tobacco-related harm derives from cigarette smoking.¹⁹⁰ Although smokeless tobacco consumption carries health risk, it is substantially less harmful than smoking.^{191,192} Places such as Sweden, which has a substantial number of snus (smokeless tobacco) users, has the lowest rate of lung cancer among developed countries.¹⁹³ The idea that ECs use can promote harm reduction is appealing, at least in theory. The idea is to substitute smoke inhalation with the substantially less toxic EC aerosol, which is devoid of combustion products and has lower amounts of known carcinogens compared with smoke.^{179,183,194,195} The concept is similar to providing methadone, buprenorphine, or clean needles to people who inject heroin. These steps do not entirely eliminate opioid-related risk, but they reduce risk substantially.^{196–198} Much of the resistance to EC use as a harm reduction strategy arises from a lack of definitive data showing effectiveness and improved outcomes in the adult smoker population, as well as concerns over effects on youth and other nonsmokers. These data, if they exist, will not be available for many years, given the relatively short duration that ECs have been in widespread use. Thus, harm reduction from EC use remains a theoretical possibility to date but remains to be proven.

There is evidence suggesting that ECs use can help some people to stop combustible cigarette smoking, both at the population and individual levels.^{199–201} Although unclear whether a causal effect, smoking rates have declined more quickly in the United States since the introduction of ECs into commercial markets, possibly indicating a substitution effect (i.e., people choosing to use ECs instead of cigarettes).²⁰² Early clinical trials examined ECs in both motivated and unmotivated cigarette smokers. These studies found smoking quit rates similar to or non-statistically higher than the nicotine patch, as well as reductions in cigarettes smoked per day.^{203,204} Study limitations included low overall smoking quit rates and the use of early-generation EC products, which likely limited the statistical power necessary to observe differences between groups.

A significant follow-up study, which is the most important to date, is a multicenter trial of 886 smokers conducted throughout the United Kingdom that directly compared second-generation ECs to traditional combination nicotine replacement (e.g., nicotine patch, gum, lozenge).²⁰¹ Both groups received behavioral counseling as part of usual care. The key study finding was that those randomized to the EC group were nearly twice as likely to achieve smoking abstinence at week 52 compared with the NRT group (18.0% vs. 9.9%; relative risk, 1.83; 95% confidence interval, 1.30–2.58), with no differences in adverse events between groups. However, 80% of subjects in the EC group were still using their EC product at the end of the study, indicating that long-term nicotine use via EC was a key factor in maintaining smoking abstinence. As noted, the long-term health effects of chronic EC use remain unclear.

E-Cigarette or Vaping Product Use-Associated Lung Injury (EVALI)

In mid-to-late 2019, the U.S. Centers for Disease Control and Prevention (CDC) began receiving reports of acute lung injury cases clinically resembling the acute respiratory distress syndrome (ARDS) (see Chapter 140) occurring in patients who reported a history of EC vaping and had no other clear cause for lung injury.²⁰⁵ The clinical syndrome commonly affected young people and resembled a systemic illness that typically resulted in fever, dyspnea, nausea/vomiting, pulmonary infiltrates, and acute respiratory failure that sometimes required mechanical ventilation.^{206–208} A wide range of pathologic patterns were reported, and the presence of lipid-laden macrophages with oil red O staining was common.^{207–209} Anecdotally, corticosteroids seemed to hasten recovery.

The discovery of this syndrome led to intense scrutiny and reporting of the new disease phenotype, subsequently named “e-cigarette or vaping product use-associated lung injury” (EVALI). A variety of ECs and vaping products were reported, making it initially difficult to pinpoint a specific cause of the epidemic. Importantly, the first case series published involving patients in Illinois and Wisconsin found that 84% of EVALI cases involved vaping of tetrahydrocannabinol (THC) oils in EC devices.²⁰⁶ THC is the main psychoactive chemical in marijuana²¹⁰ and had not been previously widely recognized as a substance consumed via EC vaping. A subsequent investigation by CDC and FDA revealed that bronchoalveolar lavage samples from EVALI patients contained vitamin E acetate, a cutting agent used to dilute THC-containing e-liquids.²¹¹ Follow-up investigations into the used products from EVALI cases seized by law enforcement revealed high proportions of illicit THC e-liquids containing vitamin E acetate.²¹² These discoveries provided strong support that EVALI was driven predominantly by vitamin E acetate-contaminated THC e-liquids, although other EC-related chemical causes of acute lung injury could not be definitively ruled out.

Practical Considerations for Clinicians Treating Patients Who Use E-Cigarettes

The clinician is very likely to encounter EC use among patients in clinical settings.²¹³ The optimal approach to these patients, many of whom may be current or former cigarette smokers and have other medical and psychiatric comorbidities,²¹⁴ can be challenging. On one hand, it is clearly best for patients to abstain from inhalation of all toxic substances, including combustible cigarettes and ECs; this is certainly a message that physicians want to convey strongly to patients. Yet, for former smokers, EC use may prevent relapse into combustible smoking and might reduce harm.²⁰¹ The severe health harms of continued cigarette smoking are well established.¹⁹⁰ Furthermore, while there have been tested approaches to smoking addiction, the optimal approach to treating vaping addiction is unknown.

Thorough social and past medical histories will help identify the patient’s level of risk, in addition to other comorbidities (i.e., mental health and other substance use disorders) that may influence the course of nicotine addiction. Routine screening for tobacco product use should include a specific question about the use of ECs and vaping. Developing an understanding of the reasons for use, the duration and frequency of use, the types of products (e.g., nicotine content, flavorings, and use of other drugs, such as THC), and where the products were obtained (e.g., authorized retailers or from informal sources such as friends) is helpful. It is important to understand whether there is dual use of combustible cigarettes and ECs and whether ECs are being used to reduce combustible use or to supplement nicotine consumption in places where smoking is forbidden. Assessing motivation to discontinue use provides an opening to encourage abstinence and trials of other treatments, such as transdermal nicotine replacement, varenicline, bupropion, and behavioral counseling.

Advice should be framed carefully, as EC use in this population may prevent relapse into cigarette smoking. It is important to note that long-term abstinence rates from cigarette smoking are low, especially for those who do not achieve abstinence for at least 3 months.²¹⁵ Thus, the population of EC users (particularly those with past or present cigarette smoking history) may represent a group with a higher level of nicotine dependence. While cessation of all inhaled substances should be encouraged, permanent and complete cessation from combustible products should be highly prioritized. If the patient is solely using ECs (and not using combustible products), it is useful to explore whether they wish to stop vaping as well. Despite a lack of evidence of effectiveness in people who vape, the combination of behavioral and pharmacologic treatments, which is the standard of care for the treatment of cigarette smoking addiction, is a reasonable starting point. It is not clear whether attempting to reduce the nicotine level in e-liquids used is a beneficial strategy to promote vaping cessation, since individuals might engage in compensatory puffing behavior (e.g., bigger or longer puffs) to maintain similar nicotine intake.²¹⁶ Longitudinal support to monitor progress and try different approaches as needed will likely be required in these patients.

What Is the Future of E-Cigarettes?

EC use will continue into the 21st century, alongside combustible cigarettes and other tobacco products. The economic growth of ECs since their inception has been staggering, yet the global demand for the products remains only a tiny fraction of the combustible cigarette market. Future trends in EC use may depend largely upon regulatory efforts, which, in turn, will be affected by public perception and opinion about the products’ relative harms and benefits. Scientific discovery will drive part of this discussion, but economic and political factors also will play a significant role.

A natural experiment in EC regulation may be emerging, as the United Kingdom has widely promoted EC use among its adult smokers for harm reduction, while other countries, such as the United States, have cracked down on the EC market more strongly in an effort to protect youth. It will be critical to understand how these different approaches affect tobacco use and health at the population level. Longitudinal trends in both combustible and noncombustible tobacco use, as well as health effects in both youth and adult populations, will provide needed insight into the effects of ECs.

CONCLUSION

Cigarette smoking is a complex social and medical issue. The physician has a particularly important role in curbing smoking. Not only must the physician participate in efforts to reduce smoking as a citizen, but as a protector of public health and a possessor of specific expertise in healthcare matters, the physician must take an active

role in health promotion. Such a role includes discouraging smoking and vaping initiation among younger patients, encouraging and assisting smoking patients to quit, and participating in social efforts designed to reduce smoking at various levels.

For individuals who are smokers, the clinician needs to approach smoking as a chronic relapsing disorder for which a range of effective treatments are available. These include nonpharmacologic and pharmacologic therapies. Optimal results can be achieved using a combined approach.

ACKNOWLEDGMENTS

The authors thank Ms. Lisa Hepp and Mr. David Daughton for assistance with prior drafts.

REFERENCES

1. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49:57–71.
2. Benowitz NL. Nicotine addiction. *N Engl J Med*. 2010;362(24): 2295–2303.
3. Baldwin IT. An ecologically motivated analysis of plant-herbivore interactions in native tobacco. *Plant Physiol*. 2001;127(4):1449–1458.
4. Fowler JS, Logan J, Wang GJ, Volkow ND. Monoamine oxidase and cigarette smoking. *Neurotoxicology*. 2003;24(1):75–82.
5. Chaudhri N, Caggiula AR, Donny EC, et al. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology (Berl)*. 2006;184(3–4):353–366.
6. Davis JA, Gould TJ. Associative learning, the hippocampus, and nicotine addiction. *Curr Drug Abuse Rev*. 2008;1(1):9–19.
7. Myers MG, Gwaltney CJ, Strong DR, et al. Adolescent first lapse following smoking cessation: situation characteristics, precipitants and proximal influences. *Addict Behav*. 2011;36(12):1253–1260.
8. Mills AL, Messer K, Gilpin EA, Pierce JP. The effect of smoke-free homes on adult smoking behavior: a review. *Nicotine Tob Res*. 2009;11(10):1131–1141.
9. Henningfield JE, Miyasato K, Jasinski DR. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. *J Pharmacol Exp Ther*. 1985;234(1):1–12.
10. Pomerleau OF. Nicotine as a psychoactive drug: anxiety and pain reduction. *Psychopharmacol Bull*. 1986;22(3):865–869.
11. McClernon FJ, Hiott FB, Westman EC, et al. Transdermal nicotine attenuates depression symptoms in nonsmokers: a double-blind, placebo-controlled trial. *Psychopharmacology (Berl)*. 2006;189(1):125–133.
12. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology (Berl)*. 2010;210(4):453–469.
13. Farsalinos KE, Romagna G, Tsiapras D, et al. Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. *Int J Environ Res Public Health*. 2013;10(6):2500–2514.
14. U.S. Department of Health, Education, and Welfare. Smoking and Health. Report of the advisory committee to the surgeon general of the public health service. Washington, DC: Office of the Surgeon General; 1964.
15. Gotti C, Clementi F. Neuronal nicotinic receptors: from structure to pathology. *Prog Neurobiol*. 2004;74(6):363–396.
16. Drenan RM, Lester HA. Insights into the neurobiology of the nicotinic cholinergic system and nicotine addiction from mice expressing nicotinic receptors harboring gain-of-function mutations. *Pharmacol Rev*. 2012;64(4):869–879.
17. Gotti C, Clementi F, Fornari A, et al. Structural and functional diversity of native brain neuronal nicotinic receptors. *Biochem Pharmacol*. 2009;78(7):703–711.
18. Changeux JP. Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. *Nat Rev Neurosci*. 2010;11(6):389–401.
19. Hajos M, Hurst RS, Hoffmann WE, et al. The selective alpha7 nicotinic acetylcholine receptor agonist PNU-282987 [N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride] enhances GABAergic synaptic activity in brain slices and restores auditory gating deficits in anesthetized rats. *J Pharmacol Exp Ther*. 2005;312(3):1213–1222.
20. Leslie FM, Mojica CY, Reynaga DD. Nicotinic receptors in addiction pathways. *Mol Pharmacol*. 2013;83(4):753–758.
21. Mansvelder HD, McGehee DS. Long-term potentiation of excitatory inputs to brain reward areas by nicotine. *Neuron*. 2000;27(2):349–357.
22. Mansvelder HD, McGehee DS. Cellular and synaptic mechanisms of nicotine addiction. *J Neurobiol*. 2002;53(4):606–617.
23. Slotkin TA, Ryde IT, Seidler FJ. Additive and synergistic effects of fetal nicotine and dexamethasone exposure on cholinergic synaptic function in adolescence and adulthood: Implications for the adverse consequences of maternal smoking and pharmacotherapy of preterm delivery. *Brain Res Bull*. 2010;81(6):552–560.
24. Goriounova NA, Mansvelder HD. Short- and long-term consequences of nicotine exposure during adolescence for prefrontal cortex neuronal network function. *Cold Spring Harb Perspect Med*. 2012;2(12):a012120.
25. Borgerding M, Klus H. Analysis of complex mixtures—cigarette smoke. *Exp Toxicol Pathol*. 2005;57(Suppl 1):43–73.
26. Henningfield JE, London ED, Benowitz NL. Arterial-venous differences in plasma concentrations of nicotine after cigarette smoking. *JAMA*. 1990;263(15):2049–2050.
27. Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev*. 2005;57(1):79–115.
28. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*. 1991;86(9): 1119–1127.
29. Lessov-Schlaggar CN, Pergadia ML, Khroyan TV, Swan GE. Genetics of nicotine dependence and pharmacotherapy. *Biochem Pharmacol*. 2008;75(1):178–195.
30. Schnoll RA, Johnson TA, Lerman C. Genetics and smoking behavior. *Curr Psychiatry Rep*. 2007;9(5):349–357.
31. Ray R, Tyndale RF, Lerman C. Nicotine dependence pharmacogenetics: role of genetic variation in nicotine-metabolizing enzymes. *J Neurogenet*. 2009;23(3):252–261.
32. Thorgeirsson TE, Gudbjartsson DF, Surakka I, et al. Sequence variants at CHRN3-CHRNA6 and CYP2A6 affect smoking behavior. *Nat Genet*. 2010;42(5):448–453.
33. Pergadia ML, Agrawal A, Loukola A, et al. Genetic linkage findings for DSM-IV nicotine withdrawal in two populations. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150B(7):950–959.
34. Liu JZ, Tozzi F, Waterworth DM, et al. Meta-analysis and imputation refines the association of 15q25 with smoking quantity. *Nat Genet*. 2010;42(5):436–440.

35. Siedlinski M, Cho MH, Bakke P, et al. Genome-wide association study of smoking behaviours in patients with COPD. *Thorax*. 2011;66(10):894–902.
36. Thorgeirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature*. 2008;452(7187):638–642.
37. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature*. 2008;452(7187):633–637.
38. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet*. 2008;40(5):616–622.
39. Pillai SG, Ge D, Zhu G, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. *PLoS Genet*. 2009;5(3):e1000421.
40. Malaiyandi V, Sellers EM, Tyndale RF. Implications of CYP2A6 genetic variation for smoking behaviors and nicotine dependence. *Clin Pharmacol Ther*. 2005;77(3):145–158.
41. Carter B, Long T, Cinciripini P. A meta-analytic review of the CYP2A6 genotype and smoking behavior. *Nicotine Tob Res*. 2004;6(2):221–227.
42. Fujieda M, Yamazaki H, Saito T, et al. Evaluation of CYP2A6 genetic polymorphisms as determinants of smoking behavior and tobacco-related lung cancer risk in male Japanese smokers. *Carcinogenesis*. 2004;25(12):2451–2458.
43. Kamataki T, Fujieda M, Kiyotani K, et al. Genetic polymorphism of CYP2A6 as one of the potential determinants of tobacco-related cancer risk. *Biochem Biophys Res Commun*. 2005;338(1):306–310.
44. Minematsu N, Nakamura H, Iwata M, et al. Association of CYP2A6 deletion polymorphism with smoking habit and development of pulmonary emphysema. *Thorax*. 2003;58(7):623–628.
45. Lerman C, Tyndale R, Patterson F, et al. Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation. *Clin Pharmacol Ther*. 2006;79(6):600–608.
46. O'Loughlin J, Paradis G, Kim W, et al. Genetically decreased CYP2A6 and the risk of tobacco dependence: a prospective study of novice smokers. *Tob Control*. 2004;13(4):422–428.
47. Guy EG, Fletcher PJ. Nicotine-induced enhancement of responding for conditioned reinforcement in rats: role of prior nicotine exposure and alpha4beta2 nicotinic receptors. *Psychopharmacology (Berl)*. 2013;225(2):429–440.
48. Escobedo LG, Anda RF, Smith PF, et al. Sociodemographic characteristics of cigarette smoking initiation in the United States. Implications for smoking prevention policy. *JAMA*. 1990;264(12):1550–1555.
49. Gilpin EA, Lee L, Evans N, Pierce JP. Smoking initiation rates in adults and minors: United States, 1944–1988. *Am J Epidemiol*. 1994;140(6):535–543.
50. Dierker L, Swendsen J, Rose J, et al. Transitions to regular smoking and nicotine dependence in the Adolescent National Comorbidity Survey (NCS-A). *Ann Behav Med*. 2012;43(3):394–401.
51. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. *Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General*. Atlanta, GA: Centers for Disease Control; 2012.
52. Freedman KS, Nelson NM, Feldman LL. Smoking initiation among young adults in the United States and Canada, 1998–2010: a systematic review. *Prev Chronic Dis*. 2012;9:E05.
53. Bernat DH, Klein EG, Forster JL. Smoking initiation during young adulthood: a longitudinal study of a population-based cohort. *J Adolesc Health*. 2012;51(5):497–502.
54. Fischer PM, Schwartz MP, Richards JW Jr, et al. Brand logo recognition by children aged 3 to 6 years. Mickey Mouse and Old Joe the Camel. *JAMA*. 1991;266(22):3145–3148.
55. Pierce JP, White VM, Emery SL. What public health strategies are needed to reduce smoking initiation? *Tob Control*. 2012;21(2):258–264.
56. Headen SW, Bauman KE, Deane GD, Koch GG. Are the correlates of cigarette smoking initiation different for black and white adolescents? *Am J Public Health*. 1991;81(7):854–858.
57. Shiffman S. Tobacco “chippers”—individual differences in tobacco dependence. *Psychopharmacology (Berl)*. 1989;97(4):539–547.
58. Shiffman S, Paty JA, Gnys M, et al. Nicotine withdrawal in chippers and regular smokers: subjective and cognitive effects. *Health Psychol*. 1995;14(4):301–309.
59. Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness: A population-based prevalence study. *JAMA*. 2000;284(20):2606–2610.
60. Kalman D, Morissette SB, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am J Addict*. 2005;14(2):106–123.
61. Myles N, Newall HD, Curtis J, et al. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. *J Clin Psychiatry*. 2012;73(4):468–475.
62. Benowitz NL, Jacob P 3rd. Intravenous nicotine replacement suppresses nicotine intake from cigarette smoking. *J Pharmacol Exp Ther*. 1990;254(3):1000–1005.
63. Benowitz NL, Jacob P 3rd, Kozlowski LT, Yu L. Influence of smoking fewer cigarettes on exposure to tar, nicotine, and carbon monoxide. *N Engl J Med*. 1986;315(21):1310–1313.
64. Benowitz NL, Jacob P 3rd. Nicotine renal excretion rate influences nicotine intake during cigarette smoking. *J Pharmacol Exp Ther*. 1985;234(1):153–155.
65. Benowitz NL, Hall SM, Herning RI, et al. Smokers of low-yield cigarettes do not consume less nicotine. *N Engl J Med*. 1983;309(3):139–142.
66. Daughton D, Fix A, Roberts D, Rennard SI. Sleep disturbance smoking: a tobacco addiction syndrome. *Am Rev Resp Dis*. 1988;137:A464.
67. Xian H, Scherrer JF, Madden PA, et al. Latent class typology of nicotine withdrawal: genetic contributions and association with failed smoking cessation and psychiatric disorders. *Psychol Med*. 2005;35(3):409–419.
68. Xian H, Scherrer JF, Madden PA, et al. The heritability of failed smoking cessation and nicotine withdrawal in twins who smoked and attempted to quit. *Nicotine Tob Res*. 2003;5(2):245–254.
69. Rostron B. Smoking-attributable mortality in the United States. *Epidemiology*. 2011;22(3):350–355.
70. Fenelon A, Preston SH. Estimating smoking-attributable mortality in the United States. *Demography*. 2012;49(3):797–818.
71. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA*. 2004;291(10):1238–1245.

72. Ezzati M, Lopez AD. Measuring the accumulated hazards of smoking: global and regional estimates for 2000. *Tob Control*. 2003;12(1):79–85.
73. Centers for Disease Control and Prevention (CDC). Consumption of cigarettes and combustible tobacco—United States 2000–2011. *MMWR Morb Mortal Weekly Rep*. 2012;61:565–569.
74. Centers for Disease Control and Prevention (CDC). Current tobacco use among middle and high school students—United States 2011. *MMWR Morb Mortal Weekly Rep*. 2012;61:581–585.
75. Centers for Disease Control and Prevention (CDC). Current cigarette use among adults—United States 2011. *MMWR Morb Mortal Weekly Rep*. 2012;61:889–894.
76. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(45):1013–1019.
77. Centers for Disease Control and Prevention (CDC). Current Cigarette Smoking Among Adults in the United States. 2021. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/. Accessed February 12, 2021.
78. Santi S, Best JA, Brown KS, Cargo M. Social environment and smoking initiation. *Int J Addict*. 1990;25(7A–8A):881–903.
79. Pierce JP, Lee L, Gilpin EA. Smoking initiation by adolescent girls, 1944 through 1988. An association with targeted advertising. *JAMA*. 1994;271(8):608–611.
80. Toll BA, Ling PM. The Virginia Slims identity crisis: an inside look at tobacco industry marketing to women. *Tob Control*. 2005;14(3):172–180.
81. Braun S, Mejia R, Ling PM, Perez-Stable EJ. Tobacco industry targeting youth in Argentina. *Tob Control*. 2008;17(2):111–117.
82. Gendall P, Hoek J, Thomson G, et al. Young adults' interpretations of tobacco brands: implications for tobacco control. *Nicotine Tob Res*. 2011;13(10):911–918.
83. Aloise-Young PA, Slater MD, Cruickshank CC. Mediators and moderators of magazine advertisement effects on adolescent cigarette smoking. *J Health Commun*. 2006;11(3):281–300.
84. National Association of Attorneys General. Tobacco Master Settlement Agreement. <https://www.naag.org/our-work/naag-center-for-tobacco-and-public-health/the-master-settlement-agreement/>. Accessed January 14, 2022.
85. National Institute on Drug Abuse, National Institutes of Health. Monitoring the Future. <http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2020.pdf>. Accessed February 21, 2021.
86. Mercken L, Moore L, Crone MR, et al. The effectiveness of school-based smoking prevention interventions among low- and high-SES European teenagers. *Health Educ Res*. 2012;27(3):459–469.
87. Aaron DJ, Dearwater SR, Anderson R, et al. Physical activity and the initiation of high-risk health behaviors in adolescents. *Med Sci Sports Exerc*. 1995;27(12):1639–1645.
88. Centers for Disease Control and Prevention. Estimates of retailers willing to sell tobacco to minors—California, August–September 1995 and June–July 1996. *MMWR Morb Mortal Wkly Rep*. 1996;45(50):1095–1099.
89. Jason LA, Ji PY, Anes MD, Birkhead SH. Active enforcement of cigarette control laws in the prevention of cigarette sales to minors. *JAMA*. 1991;266(22):3159–3161.
90. Fichtenberg CM, Glantz SA. Youth access interventions do not affect youth smoking. *Pediatrics*. 2002;109(6):1088–1092.
91. Rigotti NA, DiFranza JR, Chang Y, et al. The effect of enforcing tobacco-sales laws on adolescents' access to tobacco and smoking behavior. *N Engl J Med*. 1997;337(15):1044–1051.
92. Biner MF, Rigotti NA. Public policy for the control of tobacco-related disease. *Med Clin North Am*. 1992;76(2):515–539.
93. Chaloupka FJ, Straif K, Leon ME, et al. Effectiveness of tax and price policies in tobacco control. *Tob Control*. 2011;20(3):235–238.
94. Sen A, Wirjanto T. Estimating the impacts of cigarette taxes on youth smoking participation, initiation, and persistence: empirical evidence from Canada. *Health Econ*. 2010;19(11):1264–1280.
95. Zhang B, Cohen J, Ferrence R, Rehm J. The impact of tobacco tax cuts on smoking initiation among Canadian young adults. *Am J Prev Med*. 2006;30(6):474–479.
96. Wilson LM, Avila Tang E, Chander G, et al. Impact of tobacco control interventions on smoking initiation, cessation, and prevalence: a systematic review. *J Environ Public Health*. 2012;2012:961724.
97. Fiore M, Jaen C, Baker T. *Treating tobacco dependence: 2008 Update*. Rockville (MD): U.S. Department of Health and Human Services; 2008.
98. Centers for Disease Control and Prevention. Cigarette smoking among adults and trends in smoking cessation—United States, 2008. *MMWR Morb Mortal Wkly Rep*. 2009;58(44):1227–1232.
99. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry*. 2016;3(8):760–773.
100. Centers for Disease Control and Prevention. The Health Consequences of Smoking—50 Years of Progress. Rockville (MD): U.S. Department of Health and Human Services; 2014.
101. Fiore M, Bailey W, Cohen S. *Smoking Cessation. Guideline technical report no 18*. Rockville, MD: Agency for Health Care Policy and Research; 1996.
102. Daughton D, Susman J, Sitorius M, et al. Transdermal nicotine therapy and primary care. Importance of counseling, demographic, and participant selection factors on 1-year quit rates. The Nebraska Primary Practice Smoking Cessation Trial Group. *Arch Fam Med*. 1998;7(5):425–430.
103. Gwaltney CJ, Metrik J, Kahler CW, Shiffman S. Self-efficacy and smoking cessation: a meta-analysis. *Psychol Addict Behav*. 2009;23(1):56–66.
104. Gulliver SB, Hughes JR, Solomon LJ, Dey AN. An investigation of self-efficacy, partner support and daily stresses as predictors of relapse to smoking in self-quitters. *Addiction*. 1995;90(6):767–772.
105. Fiore M, Bailey W, Cohen S. *Treating Tobacco Use and Dependence*. Rockville (MD): US Department of Health and Human Services; 2000.
106. Prochaska JO, DiClemente CC. Stages of change in the modification of problem behaviors. *Prog Behav Modif*. 1992;28:183–218.
107. Hettema JE, Hendricks PS. Motivational interviewing for smoking cessation: a meta-analytic review. *J Consult Clin Psychol*. 2010;78(6):868–884.
108. Niaura R. Nonpharmacologic therapy for smoking cessation: characteristics and efficacy of current approaches. *Am J Med*. 2008;121(4 Suppl 1):S11–S19.
109. Borland R, Balmford J, Hunt D. The effectiveness of personally tailored computer-generated advice letters for smoking cessation. *Addiction*. 2004;99(3):369–377.

110. Houston TK, Coley HL, Sadasivam RS, et al. Impact of content-specific email reminders on provider participation in an online intervention: a dental PBRN study. *Stud Health Technol Inform.* 2010;160(Pt 2):801–805.
111. Stead LF, Perera R, Lancaster T. A systematic review of interventions for smokers who contact quitlines. *Tob Control.* 2007;16 Suppl 1:i3–i8.
112. Cinciripini PM, Wetter DW, McClure JB. Scheduled reduced smoking: effects on smoking abstinence and potential mechanisms of action. *Addict Behav.* 1997;22(6):759–767.
113. Hughes JR, Solomon LJ, Livingston AE, et al. A randomized, controlled trial of NRT-aided gradual vs. abrupt cessation in smokers actively trying to quit. *Drug Alcohol Depend.* 2010;111(1–2):105–113.
114. Lindson-Hawley N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. *Cochrane Database Syst Rev.* 2012;11:CD008033.
115. Tahiri M, Mottillo S, Joseph L, et al. Alternative smoking cessation aids: a meta-analysis of randomized controlled trials. *Am J Med.* 2012;125(6):576–584.
116. Barnes J, Dong CY, McRobbie H, et al. Hypnotherapy for smoking cessation. *Cochrane Database Syst Rev.* 2010(10):CD001008.
117. Rigotti NA. Pharmacotherapy for Smoking Cessation. *UpToDate.* 2020. <https://www.uptodate.com/contents/pharmacotherapy-for-smoking-cessation-in-adults>. Accessed February 20, 2021.
118. Hajek P, West R, Foulds J, et al. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Arch Intern Med.* 1999;159(17):2033–2038.
119. Rigotti NA. Clinical practice. Treatment of tobacco use and dependence. *N Engl J Med.* 2002;346(7):506–512.
120. Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med.* 2000;160(20):3128–3134.
121. Schneider NG, Cortner C, Gould JL, et al. Comparison of craving and withdrawal among four combination nicotine treatments. *Hum Psychopharmacol.* 2008;23(6):513–517.
122. Killen JD, Fortmann SP, Newman B, Varady A. Evaluation of a treatment approach combining nicotine gum with self-guided behavioral treatments for smoking relapse prevention. *J Consult Clin Psychol.* 1990;58(1):85–92.
123. Dautzenberg B, Nides M, Kienzler JL, Callens A. Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate lozenges (Nicotinell). *BMC Clin Pharmacol.* 2007;7:11.
124. Smith SS, McCarthy DE, Japuntich SJ, et al. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. *Arch Intern Med.* 2009;169(22):2148–2155.
125. Schnoll RA, Goelz PM, Veluz-Wilkins A, et al. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med.* 2015;175(4):504–511.
126. Pickworth WB, Bunker EB, Henningfield JE. Transdermal nicotine: reduction of smoking with minimal abuse liability. *Psychopharmacology (Berl).* 1994;115(1–2):9–14.
127. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med.* 1994;154(9):989–995.
128. Piper ME, Smith SS, Schlam TR, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Arch Gen Psychiatry.* 2009;66(11):1253–1262.
129. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev.* 2007(1):Cd000031.
130. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med.* 1997;337(17):1195–1202.
131. Swan GE, McAfee T, Curry SJ, et al. Effectiveness of bupropion sustained release for smoking cessation in a health care setting: a randomized trial. *Arch Intern Med.* 2003;163(19):2337–2344.
132. U.S. Food and Drug Administration. The smoking cessation aids varenicline (marketed as chantix) and bupropion (marketed as zyban and generics): suicidal ideation and behavior. *FDA Drug Safety Newsletter.* 2009;2:1–4.
133. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* 2016;387(10037):2507–2520.
134. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha-4beta2 nicotinic receptor partial agonist for smoking cessation. *J Med Chem.* 2005;48(10):3474–3477.
135. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha-4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296(1):47–55.
136. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296(1):56–63.
137. Tonstad S, Tonnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA.* 2006;296(1):64–71.
138. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev.* 2012(4):CD006103.
139. Hughes JR, Russ CI, Arteaga CE, Rennard SI. Efficacy of a flexible quit date versus an a priori quit date approach to smoking cessation: a cross-study analysis. *Addict Behav.* 2011;36(12):1288–1291.
140. Rennard S, Hughes J, Cinciripini PM, et al. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. *Nicotine Tob Res.* 2012;14(3):343–350.
141. Oncken C, Gonzales D, Nides M, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med.* 2006;166(15):1571–1577.
142. Gunnell D, Irvine D, Wise L, et al. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. *BMJ.* 2009;339:b3805.
143. Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ.* 2011;183(12):1359–1366.
144. Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. *BMJ.* 2012;344:e2856.
145. U.S. Food and Drug Administration. FDA Drug Safety Communication: Safety Review Update of Chantix (varenicline) and Risk of Cardiovascular Adverse Events. 2012. <http://www.fda.gov/Drugs/DrugSafety/ucm330367.htm>. Accessed January 14, 2022.

146. Moore T, Cohen M, Furberg CD. Strong safety signal seen for new varenicline risks. Horsham, PA: Institute for Safe Medication Practices; 2008.
147. U.S. Food and Drug Administration. Public Health Advisory: Important Information on Chantix (varenicline). 2013.
148. Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. *Cochrane Database Syst Rev*. 2004(3):CD000058.
149. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2012;10:CD008286.
150. Rigotti NA, Clair C, Munafó MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *Cochrane Database Syst Rev*. 2012(5):Cd001837.
151. Allen SS, Hatsukami DK, Christianson D. Nicotine withdrawal and depressive symptomatology during short-term smoking abstinence: a comparison of postmenopausal women using and not using hormone replacement therapy. *Nicotine Tob Res*. 2003;5(1):49–59.
152. Higuchi LM, Khalili H, Chan AT, et al. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. *Am J Gastroenterol*. 2012;107(9):1399–1406.
153. Broekema M, ten Hacken NH, Volbeda F, et al. Airway epithelial changes in smokers but not in ex-smokers with asthma. *Am J Respir Crit Care Med*. 2009;180(12):1170–1178.
154. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J*. 2013;41(3):716–726.
155. Buist AS, Sexton GJ, Nagy JM, Ross BB. The effect of smoking cessation and modification on lung function. *Am Rev Respir Dis*. 1976;114(1):115–122.
156. Swan GE, Hodgkin JE, Roby T, et al. Reversibility of airways injury over a 12-month period following smoking cessation. *Chest*. 1992;101(3):607–612.
157. Rigotti NA. Overview of smoking cessation management in adults. *UpToDate*. 2020. <https://www.uptodate.com/contents/overview-of-smoking-cessation-management-in-adults>. Accessed January 14, 2022.
158. Rodriguez D. Tobacco and nicotine use in pregnancy: Cessation strategies and treatment options. *UpToDate*. 2020. <https://www.uptodate.com/contents/tobacco-and-nicotine-use-in-pregnancy-cessation-strategies-and-treatment-options>. Accessed January 14, 2022.
159. Anthonisen NR, Connell JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA*. 1994;272(19):1497–1505.
160. Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet*. 2001;357(9268):1571–1575.
161. Tashkin DP, Rennard S, Hays JT, et al. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. *Chest*. 2011;139(3): 591–599.
162. Institute of Medicine Committee to Assess the Science Base for Tobacco Harm Reduction. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: National Academy of Science; 2001.
163. Rodu B. The scientific foundation for tobacco harm reduction, 2006–2011. *Harm Reduct J*. 2011;8:19.
164. Rennard SI, Daughton D, Fujita J, et al. Short-term smoking reduction is associated with reduction in measures of lower respiratory tract inflammation in heavy smokers. *Eur Respir J*. 1990;3(7):752–759.
165. Millatmal T, Daughton D, Thompson AB, et al. Smoking reduction: an alternative approach for smokers who cannot quit. *Monaldi Arch Chest Dis*. 1994;49(5):421–424.
166. Mahmarian JJ, Moye LA, Nasser GA, et al. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. *J Am Coll Cardiol*. 1997;30(1):125–130.
167. Jarvis MJ, Boreham R, Primatesta P, et al. Nicotine yield from machine-smoked cigarettes and nicotine intakes in smokers: evidence from a representative population survey. *J Natl Cancer Inst*. 2001;93(2):134–138.
168. Strasser AA, Lerman C, Sanborn PM, et al. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug Alcohol Depend*. 2007;86(2–3): 294–300.
169. Company RR. *New Cigarette Prototypes that Heat Instead of Burn Tobacco*. Winston-Salem, NC: RJ Reynolds Tobacco Company; 1988.
170. Schraufnagel DE, Blasi F, Drummond MB, et al. Electronic cigarettes. A position statement of the forum of international respiratory societies. *Am J Respir Crit Care Med*. 2014;190(6): 611–618.
171. Drummond MB, Upson D. Electronic cigarettes. Potential harms and benefits. *Ann Am Thorac Soc*. 2014;11(2):236–242.
172. Rennard SI, Umino T, Millatmal T, et al. Evaluation of sub-clinical respiratory tract inflammation in heavy smokers who switch to a cigarette-like nicotine delivery device that primarily heats tobacco. *Nicotine Tob Res*. 2002;4(4):467–476.
173. Hansson J, Galanti MR, Hergens MP, et al. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. *Eur J Epidemiol*. 2012;27(10): 771–779.
174. Nordinval C, Nilsson PJ, Ye W, et al. Tobacco use and cancer survival: a cohort study of 40,230 Swedish male construction workers with incident cancer. *Int J Cancer*. 2013;132(1): 155–161.
175. Areffalk G, Hergens MP, Ingelsson E, et al. Smokeless tobacco (snus) and risk of heart failure: results from two Swedish cohorts. *Eur J Prev Cardiol*. 2012;19(5):1120–1127.
176. Lee PN. Summary of the epidemiological evidence relating snus to health. *Regul Toxicol Pharmacol*. 2011;59(2):197–214.
177. National Academies of Sciences, Engineering, and Medicine. *Public Health Consequences of E-Cigarettes*. Washington, DC: The National Academies Press; 2018.
178. Hajek P, Etter J-F, Benowitz N, et al. Electronic cigarettes: Review of use, content, safety, effects on smokers, and potential for harm and benefit. *Addiction*. 2014;109(11):1801–1810.
179. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control*. 2014;23(2):133–139.
180. Hon L. Electronic cigarette. Google Patents; 2013.
181. Cahn Z, Siegel M. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? *J Public Health Policy*. 2011;32(1):16–31.
182. Benowitz NL. Emerging nicotine delivery products. Implications for public health. *Ann Am Thorac Soc*. 2014;11(2):231–235.
183. Shahab L, Goniewicz ML, Blount BC, et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: A cross-sectional study. *Ann Intern Med*. 2017.

184. England LJ, Bunnell RE, Pechacek TF, et al. Nicotine and the developing human: a neglected element in the electronic cigarette debate. *Am J Prev Med.* 2015;49(2):286–293.
185. Berry KM, Fetterman JL, Benjamin EJ, et al. Association of electronic cigarette use with subsequent initiation of tobacco cigarettes in US youths. *JAMA Network Open.* 2019;2(2):e187794.
186. Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the “e-cigarette.” American Public Health Association; 2010.
187. Chand HS, Muthumalage T, Maziak W, Rahman I. Pulmonary toxicity and the pathophysiology of electronic cigarette, or vaping product, use associated lung injury. *Front Pharmacol.* 2019;10.
188. Spindle TR, Bonn-Miller MO, Vandrey R. Changing landscape of cannabis: novel products, formulations, and methods of administration. *Curr Opin Psychol.* 2019;30:98–102.
189. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *MMWR Morb Mortal Weekly Rep.* 2019;68(45):1013.
190. Centers for Disease Control and Prevention. The Health Consequences of Smoking—50 Years of Progress. Rockville (MD): U.S. Department of Health and Human Services; 2014.
191. Boffetta P, Hecht S, Gray N, et al. Smokeless tobacco and cancer. *Lancet Oncol.* 2008;9(7):667–675.
192. Levy DT, Mumford EA, Cummings KM, et al. The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: estimates of a panel of experts. *Cancer Epidemiol Biomarkers Prev.* 2004;13(12):2035–2042.
193. Foulds J, Ramstrom L, Burke M, Fagerstrom K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob Control.* 2003;12(4):349–359.
194. Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of toxicant and carcinogen metabolites in the urine of E-cigarette users versus cigarette smokers. *Nicotine Tob Res.* 2015;17(6):704–709.
195. Stephens WE. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. *Tob Control.* 2018;27(1):10–17.
196. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine–naloxone maintenance therapy for opioid dependence. *N Engl J Med.* 2006;355(4):365–374.
197. Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harv Rev Psychiatry.* 2015;23(2):63–75.
198. Drucker E, Lurie P, Wodak A, Alcabes P. Measuring harm reduction: the effects of needle and syringe exchange programs and methadone maintenance on the ecology of HIV. *AIDS.* 1998;12(Suppl A):S217–S230.
199. Zhu S-H, Zhuang Y-L, Wong S, et al. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *BMJ.* 2017;358:j3262.
200. Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine Tob Res.* 2015;17(2):127–133.
201. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. *N Engl J Med.* 2019.
202. Jamal A, Homa DM, O’Connor E, et al. Current cigarette smoking among adults—United States, 2005–2014. *MMWR Morb Mortal Weekly Rep.* 2015;64(44):1233–1240.
203. Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PloS One.* 2013;8(6):e66317.
204. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet.* 2013;382(9905):1629–1637.
205. Centers for Disease Control and Prevention. Outbreak of Lung Disease Associated with E-Cigarette Use, or Vaping. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed January 14, 2022.
206. Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related to E-cigarette use in Illinois and Wisconsin—preliminary report. *N Engl J Med.* 2020;382(10):903–916.
207. Davidson K. Outbreak of electronic-cigarette-associated acute lipoid pneumonia—North Carolina, July–August 2019. *MMWR Morb Mortal Weekly Rep.* 2019;68(36):784–786.
208. Lewis N. E-cigarette use, or vaping, practices and characteristics among persons with associated lung injury—Utah, April–October 2019. *MMWR Morb Mortal Weekly Rep.* 2019;68(42):953–956.
209. Butt YM, Smith ML, Tazelaar HD, et al. Pathology of vaping-associated lung injury. *N Engl J Med.* 2019;381(18):1780–1781.
210. Koppel BS, Brust JCM, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2014;82(17):1556–1563.
211. Blount BC, Karwowski MP, Morel-Espinosa M, et al. Evaluation of bronchoalveolar lavage fluid from patients in an outbreak of E-cigarette, or Vaping, product use-associated lung injury—10 states, August–October 2019. *MMWR Morb Mortal Weekly Rep.* 2019;68(45):1040–1041.
212. Taylor J, Wiens T, Peterson J, et al. Characteristics of e-cigarette, or vaping, products used by patients with associated lung injury and products seized by law enforcement—Minnesota, 2018 and 2019. *MMWR Morb Mortal Weekly Rep.* 2019;68(47):1096.
213. Baldassarri SR, Chupp GL, Leone FT, et al. Practise patterns and perceptions of chest health care providers on electronic cigarette use: an in-depth discussion and report of survey results. *J Smok Cessat.* 2018;13(2):72–77.
214. Rojewski AM, Baldassarri S, Cooperman NA, et al. Exploring issues of comorbid conditions in people who smoke. *Nicotine Tob Res.* 2016;18(8):1684–1696.
215. Gilpin EA, Pierce JP, Farkas AJ, Farkas AJ. Duration of smoking abstinence and success in quitting. *J Natl Cancer Inst.* 1997;89(8):572.
216. Baldassarri SR, Hillmer AT, Anderson JM, et al. Use of electronic cigarettes leads to significant beta2-nicotinic acetylcholine receptor occupancy: evidence from a PET imaging study. *Nicotine Tob Res.* 2017;20(4):425–433.

CHAPTER 42

Rehabilitation in Chronic Obstructive Pulmonary Disease and Other Respiratory Disorders

Andrew L. Ries

Duc M. Ha

INTRODUCTION

Rehabilitation for patients with chronic lung diseases is well established as a means of enhancing standard pharmacologic and other therapies in controlling and alleviating symptoms and optimizing functional capacity.^{1–5} The primary goal of any rehabilitation program is to restore the patient to the highest possible level of independent function. This goal is accomplished by helping patients and significant others learn more about the underlying disease, treatment options, and coping strategies. Patients are encouraged to participate actively in providing their own health care, become more independent in daily activities, and be less dependent on health professionals and expensive medical resources. Rather than addressing solely reversal of the disease process, rehabilitation focuses on improving disability from disease.

Historically, pulmonary rehabilitation strategies were developed and used primarily for patients with chronic obstructive pulmonary disease (COPD). However, pulmonary rehabilitation has also been applied successfully to patients with other chronic lung conditions, including interstitial lung diseases, asthma, cystic fibrosis, bronchiectasis, pulmonary hypertension, and thoracic cage abnormalities.^{3,5–7} Also, among patients with lung cancer, rehabilitation prior to resectional surgery improves exercise capacity and may reduce perioperative complications and length of hospital stay.⁸ Following surgery, rehabilitation can mitigate the adverse effects of treatment and improve physical function and symptom control, especially if initiated early.^{9–12} Patients with advanced lung cancer can also experience improvements in exercise capacity with training.¹³

Pulmonary rehabilitation has been used successfully in the evaluation and preparation of patients for surgery, such as lung transplantation and lung volume reduction surgery, and in maximizing recovery after surgery.^{14–16} Pulmonary rehabilitation has also been used to facilitate patient recovery from acute processes such as acute lung injury, or exacerbations of chronic lung disease requiring mechanical ventilation or acute hospital care. The 2020 worldwide COVID-19 pandemic highlights the needs and potential benefits of pulmonary rehabilitation for the large number of patients recovering from lung injury.¹⁷

Pulmonary rehabilitation is appropriate for any patient with stable lung disease who is disabled by respiratory symptoms. Even patients with advanced disease may benefit if they are selected appropriately and realistic goals are set.

This chapter defines pulmonary rehabilitation and outlines issues related to patient selection and evaluation. There is also discussion of key components of a pulmonary rehabilitation program, results and benefits of pulmonary rehabilitation, the use of pulmonary rehabilitation in various conditions and settings, and, finally, the role of rehabilitation as an adjunct to lung surgery.

DEFINITION

In 2013, the American Thoracic Society and European Respiratory Society adopted the following definition:

“Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors.”³

This definition highlights three important features of successful rehabilitation. First, the program is *multidisciplinary*. Pulmonary rehabilitation programs utilize expertise from various healthcare disciplines that is integrated into a comprehensive, cohesive program tailored to the needs of each patient. Second, the program is tailored to the *individual*. Patients with disabling lung disease require individual assessment of needs, individual attention, and a program designed to meet realistic individual goals. Third, the program addresses *multidimensional health issues* including physical, psychological, and social function as well as healthcare utilization.

The team of healthcare professionals in pulmonary rehabilitation may include physicians, nurses, respiratory and physical therapists, mental health professionals, exercise specialists, and others with appropriate expertise. The specific team make-up depends upon the resources and expertise available, but it usually includes at least one full-time staff member. Responsibilities of team members generally cross disciplines.¹⁸

Within this general framework, successful pulmonary rehabilitation programs have been established in both outpatient and inpatient settings and with different formats. A key to success is a dedicated, enthusiastic staff that is familiar with respiratory problems and can relate well to pulmonary patients and motivate them.

PATIENT SELECTION

Any patient with symptomatic chronic lung disease is a candidate for pulmonary rehabilitation (Table 42-1).¹⁹ Appropriate patients are aware of disability from their disease and motivated to participate actively in their own care to improve their health status. Patients with mild chronic disease may not perceive their symptoms to be severe enough to warrant a comprehensive care program. On the other hand, patients with severe disease who are bed bound may be too limited to benefit greatly.

Criteria based on arbitrary lung function parameters or age alone should not be used in selecting patients.⁴ Pulmonary function alone is not a good predictor of symptoms, function, or improvement after rehabilitation. Chronic lung disease is commonly associated with systemic features that contribute to functional limitations and may

TABLE 42-1 Patient Selection Criteria for Pulmonary Rehabilitation

| |
|--|
| Symptomatic chronic lung disease |
| Stable on standard therapy |
| Functional limitation from disease |
| Relationship with primary care provider |
| Motivated to be actively involved in and take responsibility for own health care |
| No other interfering or unstable medical conditions |
| No arbitrary lung function or age criteria |

benefit from rehabilitation.²⁰ In general, selection should be based upon a person's disability from their disease, potential for improvement, and motivation to participate actively in a comprehensive self-care program. Also, pulmonary rehabilitation is not a primary mode of therapy. Patients should be stabilized on standard medical therapy and should not have other disabling or unstable conditions that might limit their ability to participate fully in the program and to concentrate on the necessary tasks.

The ideal patient for pulmonary rehabilitation, then, is one with functional limitation from moderate to severe lung disease who is stable on standard therapy, not distracted or limited by other serious or unstable medical conditions, willing and able to learn about his or her disease, and motivated to devote the time and effort necessary to benefit from a comprehensive care program.

PATIENT EVALUATION

The initial step is screening patients to ensure appropriate selection and to set realistic individual and program goals. The evaluation process includes the following components: interview, medical evaluation, psychosocial assessment, diagnostic testing, and goal setting (Table 42-2).

■ Interview

The screening interview is an important first step. It serves to introduce the patient to the program, review the medical history, and identify psychosocial problems and needs. Family members and significant others should be included. Communication with the primary care provider is important to establish the vital link for the rehabilitation staff to clarify medical questions prior to the program and facilitate subsequent recommendations. Care and attention in this initial evaluation helps in setting goals compatible with everyone's expectations as well as appropriate programmatic objectives.

■ Medical Evaluation

Reviewing medical history helps to identify the patient's lung disease and assess its severity. Other medical problems that might preclude or delay participation may be identified. Available laboratory data should be reviewed, including pulmonary function and

exercise tests, rest and exercise arterial blood gas measurements, chest radiographs, electrocardiogram, and pertinent blood tests. Program staff can then determine the need for any additional information or action before the program begins.

■ Psychosocial Assessment

Successful rehabilitation requires attention not only to the patient's physical problems but also to psychological, emotional, and social issues. Patients with chronic illnesses experience psychosocial difficulties as they struggle to deal with symptoms they may not fully understand.²¹

Neuropsychological impairment is common in patients with chronic lung diseases and cannot be accounted for solely on the basis of age, depression, or organic disease. Commonly, such patients become depressed, frightened, anxious, and more dependent on others to care for their needs. Progressive dyspnea is a frightening symptom and may lead to a vicious "fear-dyspnea" cycle: With progressive disease, less exertion results in more dyspnea, which produces more fear and anxiety, which, in turn, lead to more dyspnea. Ultimately, the patient avoids any physical activity associated with both of these unpleasant symptoms.

In addressing these problems, the initial evaluation should assess the patient's psychological state and pay attention to "psychosocial clues" that may be apparent during the screening interview (e.g., level of family and social support, the patient's living arrangement, activities of daily living, hobbies, and employment potential). Important clues in initial interviews to the patient's emotional state may be evident in nonverbal communication, such as facial expression, physical appearance, handshake, and personal space (distance between individuals when conversing). Cognitive impairment that may limit the patient's ability to participate fully in the rehabilitation program may be identified. Family members and significant others may provide valuable insight and should be included in the screening process and program whenever possible.

■ Diagnostic Testing

Planning an appropriate rehabilitation program requires accurate, current information. The complexity of the testing procedures performed depends upon individual patient and program goals as well as the facilities and expertise available.

Pulmonary function testing is used to characterize lung disease and quantify impairment. Spirometry and lung volume measurements are most useful. Other tests (e.g., diffusing capacity, maximal respiratory pressures to assess muscle strength) can be added as needed.

Exercise testing helps to assess the patient's exercise tolerance and to evaluate changes in arterial blood gases (e.g., hypoxemia or hypercapnia) with exercise.^{22,23} This may also uncover coexisting diseases (e.g., heart disease). The exercise test is also used to establish a safe and appropriate prescription for subsequent training.

Maximal exercise of patients with chronic lung disease is limited largely by their breathing reserve, although chronic lung diseases are increasingly recognized as being associated with systemic effects that may also contribute to exertional symptoms (e.g., muscle fatigue). Simple pulmonary function tests such as spirometry can be used to estimate a patient's capacity for sustained breathing (maximal ventilation) during exercise. The forced expiratory volume in 1 second (FEV₁) is most useful in this regard. However, lung function only provides an estimate of an individual patient's maximum work capacity. Exercise tolerance depends also on the patient's perception and tolerance of the subjective symptom of breathlessness. Therefore, it is important to exercise patients to assess their physical function and symptom tolerance.

Exercise evaluation for rehabilitation is most easily performed with the type of activity planned for training (e.g., treadmill for a

TABLE 42-2 Components of a Comprehensive Pulmonary Rehabilitation Program

| |
|---|
| Patient evaluation |
| Interview |
| Medical evaluation |
| Psychosocial assessment |
| Diagnostic testing |
| Pulmonary function |
| Exercise |
| Arterial blood gases/oximetry |
| Goal setting |
| Program content |
| Education |
| Respiratory and chest physiotherapy instruction |
| Bronchial hygiene |
| Breathing retraining techniques |
| Oxygen |
| Exercise |
| Psychosocial support |

walking training program). Laboratory exercise testing is most commonly performed using either (1) rapid, progressive, incremental levels to a symptom-limited maximum or (2) defined steady-state levels.^{22,24} The former is most useful for determining exercise tolerance and the limitations to maximum performance. The latter may be preferred for assessing training prescriptions. Simpler exercise tests, such as the 6-minute walk test, have been used increasingly in recent years to measure exercise tolerance outside of a laboratory setting.²⁵ These timed distance walk tests measure the maximum distance a person can walk within a defined period (e.g., 6 minutes). Such tests have the advantage of requiring less equipment and technical expertise; however, attention must be paid to the details of testing procedures because variations in factors such as the walking course, patient instructions, encouragement during tests, use of oxygen or monitoring devices, and number of tests performed will influence the results. Also, these tests do not provide the detailed physiologic data typically included in more formal laboratory exercise tests.

Measurement of arterial blood gases at rest and during exercise is important because of the frequent but unpredictable occurrence of exercise-induced hypoxemia.²⁶ Arterial blood gas sampling during exercise makes testing more complex. The noninvasive estimate of arterial oxygen saturation by cutaneous (e.g., pulse) oximetry is useful for continuous monitoring, but it has limited accuracy (95% confidence limits, $\pm 4\%-5\%$).²⁷

■ Goals

After a patient's medical, physiologic, and psychosocial state have been evaluated, specific goals should be set that are compatible with his or her disease, needs, and expectations. Goals should be realistic in light of the program objectives. Family members and significant others should be included so that all understand what can and cannot be achieved. Programs should evaluate individual patients to document changes before and after pulmonary rehabilitation with standardized outcome measures of exercise tolerance (e.g., 6-minute walk distance) and symptoms (e.g., dyspnea) or health status (e.g., health-related quality of life).

PROGRAM CONTENT

Comprehensive pulmonary rehabilitation programs typically include several key components: education, instruction in respiratory and chest physiotherapy, psychosocial support, and exercise training (*Table 42-2*). Often, the various components are provided simultaneously; for example, during an exercise session, a patient may learn and practice breathing techniques for symptom control while being encouraged and supported by staff or other patients. Although there is no consensus regarding the optimal duration of a pulmonary rehabilitation intervention, typical programs last 6 to 12 weeks with 2 to 3 sessions per week, each session including several hours of supervised exercise training and individual or group education and psychosocial interventions.

■ Education

Successful pulmonary rehabilitation depends upon an understanding of lung disease and active involvement by patients and important others in providing social support. Education is an integral component; even patients with severe disease can gain a better understanding of their disease and learn specific means to deal with problems. Instruction can be provided individually or in small groups, but it should be adapted to different learning abilities. Topics discussed commonly include normal lung function, chronic lung disease, medications, nutrition, travel, stress reduction and relaxation, reasons to call the physician, and planning a daily schedule. Individual instruction and coaching may be provided on the use of respiratory

therapy equipment and supplemental oxygen, breathing techniques, bronchial drainage, chest percussion, energy-saving techniques, and self-care tips. The general philosophy is to encourage patients to assume responsibility for their own care and become partners with their physician in providing the care.²⁸

Despite the importance of education, it is unlikely that increased patient knowledge alone will lead to improved health status. It is more difficult to change attitudes and behaviors. Patients require specific, individualized treatment strategies, instruction, and reinforcement. Thus, education is a necessary but not sufficient component of pulmonary rehabilitation.

■ Respiratory and Chest Physiotherapy Techniques

Patients with chronic lung disease use, abuse, and are confused about respiratory and chest physiotherapy techniques. In pulmonary rehabilitation, each patient's needs for respiratory care techniques should be assessed and instruction provided in proper use. These techniques may include chest physiotherapy to control secretions, breathing retraining techniques to relieve and control dyspnea and improve ventilatory function, and proper use and care of respiratory equipment including nebulizers, metered dose inhalers, and supplemental oxygen.

■ Bronchial Hygiene

Patients with chronic lung diseases frequently have abnormal lung clearance mechanisms that increase problems with retained secretions and infection. Therefore, rehabilitation programs teach a variety of chest physiotherapy techniques for secretion control (e.g., coughing, postural drainage, chest vibration, and percussion). These are important for patients who experience excess mucus production during exacerbations as well as for those with chronic sputum production. The use of mucolytic agents to reduce viscosity of secretions is of questionable benefit.^{29,30}

■ Breathing Retraining Techniques

Pulmonary rehabilitation typically includes instruction in breathing techniques, such as diaphragmatic and pursed lips breathing—techniques aimed at helping patients relieve and control breathlessness, improve their ventilatory pattern (i.e., slowed respiratory rate and increased tidal volume), prevent dynamic airway compression, improve respiratory synchrony of the abdominal and thoracic musculature, and improve gas exchange.³¹ Review of studies evaluating these techniques indicates that improvement in symptoms (e.g., dyspnea) is a more consistent finding than are measurable changes in physiologic parameters. The diaphragmatic breathing technique is a maneuver in which the patient consciously coordinates abdominal wall expansion with inspiration and slows expiration through pursed lips. The primary effect is to slow respiratory rate and increase tidal volume. Pursed-lip breathing is commonly taught to pulmonary patients, particularly those with COPD. This technique was observed by Laennec as early as 1830 and advocated as a physical exercise for pulmonary patients in the early part of the twentieth century. As a maneuver assumed naturally by many patients with respiratory disease, pursed-lip breathing is characterized by tensing the lips and narrowing the mouth opening during expiration. The aim is to slow expiration and maintain positive airway pressure to "stent the airways open" and prevent collapse.³²

■ Oxygen

When chronic oxygen therapy is required, available delivery methods should be reviewed to help select the best system for the patient's needs. Supplemental oxygen is beneficial for patients with severe resting hypoxemia. Long-term continuous oxygen therapy has been clearly shown to improve survival and reduce mortality

and morbidity in hypoxic patients with COPD.^{33,34} The benefits of supplemental oxygen for nonhypoxic patients or those with intermittent hypoxemia (e.g., during exercise or sleep) are less clearly defined. Although continuous oxygen therapy is feasible and safe, maintaining patients on supplemental oxygen presents several challenges. Handling equipment is particularly difficult for physically disabled and frail patients. Therefore, it is important to assess each person's oxygen needs and provide appropriate instruction.^{35,36}

Several new developments have improved the efficiency of gas delivery systems and patient compliance with continuous oxygen therapy. Liquid oxygen provides more gas with less weight than tanks of compressed gas, particularly in portable systems. Oxygen-conserving devices may increase the efficiency of delivery, reducing flow requirements and prolonging the life span of portable gas sources. Transtracheal oxygen delivery may help to improve compliance and avoid problems with nasal catheters; however, patients must be instructed carefully in caring for the catheter.³⁷

■ Exercise

Exercise is important in pulmonary rehabilitation.³⁸ Considerable evidence supports favorable responses to exercise training in patients with chronic lung diseases.^{5,36} Benefits are both physiologic and psychological. Patients may increase their maximum capacity and endurance for physical activity, even though objective measures of lung function do not usually change. Patients may also benefit from learning to perform physical tasks more efficiently. Exercise training provides an ideal opportunity for patients to learn their capacity for physical work and use and practice methods for controlling dyspnea (e.g., breathing and relaxation techniques). Of all the components in a comprehensive pulmonary rehabilitation program, exercise is probably the most costly and labor-intensive, considering the personnel, equipment, and expertise required. Principles of exercise for patients with lung disease differ from those based on normals or other patient populations because of differences in the limitations to exercise and the problems encountered in training.

Many approaches have been used to train the person with chronic lung disease. To be successful, the program should be tailored to the individual's physical abilities, interests, resources, and environment. For general application, techniques should be simple and inexpensive. As in normals and other patients, benefits are largely specific to the muscles and tasks involved in training. Patients tend to do best with activities and exercises for which they are trained. Walking programs are particularly useful. They have the added benefit of encouraging patients to expand social horizons. In inclement weather, many can walk indoors (e.g., at shopping malls). Other types of exercise (e.g., cycling, swimming) also are effective. Patients should be encouraged to incorporate regular exercise into daily activities they enjoy (e.g., golf, gardening). Since many persons with chronic lung disease have limited exercise tolerance, emphasis during training should be placed on increasing endurance. Changes in endurance with rehabilitation are often greater than changes in maximal exercise tolerance and allow patients to become more functional within their physical limits. Increase in maximum exercise is also possible as patients gain experience and confidence. Resistive training is also used commonly in rehabilitation and can lead to significant increases in muscle strength that are important for many activities of daily living.^{36,39}

■ Exercise Prescription

Selecting a training target based upon a predetermined percentage of predicted maximal heart rate or ($\dot{V}O_2$) is a well-established practice for normals or patients without underlying pulmonary disease. However, in patients with chronic lung diseases, the best method of choosing an appropriate training prescription is less clearly defined. Exercise tolerance in pulmonary patients is typically limited by

maximal achievable ventilation and breathlessness. Such patients frequently do not reach their limits of cardiac or peripheral muscle performance.

Much controversy exists regarding the appropriate training intensity target for patients with chronic lung disease. Use of a target heart rate has been advocated by some, although it is recognized that such a target may not be reliable for patients with more severe disease. Many patients with lung disease can be trained at a high percentage of maximal exercise tolerance, with work levels approaching or even exceeding the maximal level reached on the initial exercise test. In a study of 52 patients with moderate to severe COPD, patients were able to perform endurance exercise testing at an average workload of 95% of their baseline maximum.⁴⁰ After 8 weeks of training, these patients were training at 86% of the baseline maximum. In fact, many patients with severe COPD were exercising at levels exceeding their baseline maximum. In another study that examined 59 patients with moderate to severe COPD who trained at levels near their ventilatory limits, a mean peak exercise ventilation of 100% of measured maximal voluntary ventilation was achieved after 12 days of training and at 3 months of follow-up.⁴¹ These findings suggest that even patients with advanced disease can be trained successfully at or near maximal exercise levels.

Based on the findings noted previously, some pulmonary rehabilitation programs define exercise targets and progression during training more by symptom tolerance than heart rate, work level, or other physiologic measurements. Ratings of perceived symptoms (e.g., breathlessness) help teach patients to exercise to "target" levels of breathing discomfort. A typical approach is to begin training at a level that the patient can sustain with reasonable comfort for several minutes and then to increase the time or exercise level according to symptom tolerance. Patients are encouraged to exercise daily and increase exercise duration up to 15 to 30 min of continuous activity. This graduated program helps patients to achieve a goal of improved tolerance for tasks of daily living, which often require a period of sustained activity.

■ Blood Gas Changes

A major problem in planning a safe exercise program for patients with lung disease is the potential for worsening of hypoxemia with exercise. Patients who are not hypoxic at rest may develop changes in arterial oxygenation that cannot be predicted reliably from resting measurements of pulmonary function or gas exchange.²⁶ Normal individuals do not become hypoxic with exercise. In patients with obstructive lung disease, Pa_{O_2} changes unpredictably during exercise. In patients with mild COPD, Pa_{O_2} typically does not change with exercise; in fact, it may even improve. However, in patients with moderate to severe COPD, Pa_{O_2} may increase, decrease, or remain the same. Patients with interstitial lung disease commonly develop worsening oxygenation with exercise.

Based on these observations, it is important to evaluate a patient's oxygenation status both at rest and during exercise. Such testing is also used to prescribe oxygen therapy at rest and with physical activity. With the availability of convenient, portable systems for ambulatory oxygen delivery, hypoxemia is not a contraindication to safe exercise training.

■ Other Types of Exercise

Exercise programs for pulmonary patients typically emphasize lower extremity training (e.g., walking or cycling). Since exercise conditioning is largely specific to the muscles and tasks involved in training, other forms of exercise may be particularly valuable for persons with chronic lung diseases.

Upper Extremity Training

Many patients with chronic lung disease report disabling dyspnea with daily activities involving the upper extremities (e.g., lifting,

grooming) at much lower work levels than with the lower extremities. Upper extremity exercise is accompanied by a higher ventilatory demand for a given level of work than is lower extremity exercise. Given the aforementioned muscle specificity of training, upper extremity exercises may be important in helping pulmonary patients cope better with common daily activities.⁴²

Ventilatory Muscle Training

The potential role of ventilatory muscle fatigue as a cause of respiratory failure and ventilatory limitation in patients with chronic lung disease has stimulated attempts to train the ventilatory muscles. Techniques of isocapnic hyperventilation, inspiratory resistive loading, and inspiratory threshold loading have been shown to improve function of the respiratory muscles in both normals and patients. In normals, respiratory muscle function does not limit exercise tolerance; therefore, specific respiratory muscle training is unlikely to be of clinical benefit. In patients with COPD, the patient group most extensively studied, improvement in general exercise performance from ventilatory muscle training alone has not been demonstrated consistently. Thus, the role of respiratory muscle training as a routine component of pulmonary rehabilitation has not been clearly established.

■ Psychosocial Support

An essential component of pulmonary rehabilitation is psychosocial support, the goal of which is to help patients combat progressive feelings of hopelessness and an inability to cope with chronic, progressive disease.²¹ Depression is common in patients with chronic pulmonary disorders, as are anxiety (especially anxiety over dyspnea), denial, anger, and isolation. Patients become sedentary and dependent upon family members, friends, and medical services to provide for their needs. Excessive concern over other physical problems and psychosomatic complaints arise. Sexual dysfunction and fear are common and represent often unspoken consequences of chronic lung disease. Patients may also demonstrate cognitive and neuropsychological dysfunction, possibly related to or exacerbated by the effects of hypoxemia on the brain.

Psychosocial support is provided best by a warm and enthusiastic staff who can communicate effectively with patients and devote the time and effort necessary to understand and motivate them. Family members and significant others should be included in activities so that they can understand the disease and help the patient cope. Support groups also are effective. Patients with severe psychological disorders may benefit from individual counseling and therapy. Psychotropic drugs should generally be reserved for patients with more severe psychological dysfunction.

BENEFITS OF PULMONARY REHABILITATION

Pulmonary rehabilitation is an established effective management strategy for people with COPD that improves functional and maximal exercise capacity and health-related quality of life.^{1–3,5} It also effectively alleviates dyspnea and fatigue, enhances the sense of disease control, and improves emotional functioning (Table 42-3). Traditionally, pulmonary rehabilitation is thought to be beneficial only for patients with stable disease. However, in more recent years, rehabilitation has been demonstrated to have an important role for those recovering from acute disease. In a landmark study, Man and coworkers recruited 42 patients within 10 days of discharge from hospitalizations for COPD exacerbations to undergo an 8-week pulmonary rehabilitation program.⁴³ Compared with usual care, patients who underwent pulmonary rehabilitation experienced large and clinically meaningful improvements in exercise capacity and health-related quality of life. Subsequent trials have replicated these findings, additionally demonstrate benefits towards reducing hospital readmission (Fig. 42-1) and possibly mortality risks.^{44–47}

TABLE 42-3 Results of Pulmonary Rehabilitation

| | |
|-----------------------------|--|
| Decreases in | Medical resource utilization (e.g., hospitalizations, emergency room visits) Respiratory symptoms (e.g., breathlessness) Psychological symptoms (e.g., depression, fear) |
| Increases in | Quality of life Physical activity Exercise tolerance (endurance, maximal level of activities of daily living, strength) Knowledge Independence |
| Return to work possible | |
| No change in lung function | |
| Possible prolonged survival | |

The mechanisms for benefits are multifactorial and include mitigating hospital-associated disability and reversing the negative consequences of disease exacerbation on muscle and cognitive function, comorbidity control, and self-efficacy.⁴⁸ Therefore, pulmonary rehabilitation is an important therapy that spans across the life course and disease severity for people with COPD, to reduce morbidity and possibly mortality.

Benefits and cost savings associated with pulmonary rehabilitation have been demonstrated not only in highly specialized centers, but also in community-based practice settings.^{3,5,49} A collaborative study of 647 patients in 10 centers in California reported significant improvements in dyspnea and health-related quality of life along with substantial reduction in measures of healthcare utilization over 18 months of follow-up (Fig. 42-2).⁵⁰ Similar findings with a reduction in hospital and intensive care unit days in the year after compared with the year before pulmonary rehabilitation were reported by a consortium of 11 centers in Connecticut and New York in 128 patients.⁵¹ Overall, among treatment options for patients with COPD, pulmonary rehabilitation has been shown to be very cost-effective (Fig. 42-3).⁵²

PULMONARY REHABILITATION AND LUNG SURGERY

In recent years, surgical options for patients with severe, disabling lung disease have expanded. Lung surgery in these patients represents new challenges and may further compromise already reduced lung function. Pulmonary rehabilitation has been found to be a valuable adjunct in preparing the patient for surgery or in postsurgery recovery.

■ Lung Transplantation

Pulmonary rehabilitation is recommended and used commonly in both the preoperative and postoperative phases of lung transplantation programs.¹⁴ Although the general strategies of rehabilitation may be similar, the individual and program goals and specific program components differ.

■ Pretransplant Rehabilitation

Patients with advanced lung disease who are candidates for lung transplantation are usually evaluated by the transplant team and then referred for pulmonary rehabilitation after their transplant candidacy is approved. Rehabilitation staff evaluate the patient to assess needs and plan an appropriate program that can be maintained throughout a waiting period, which may last months to

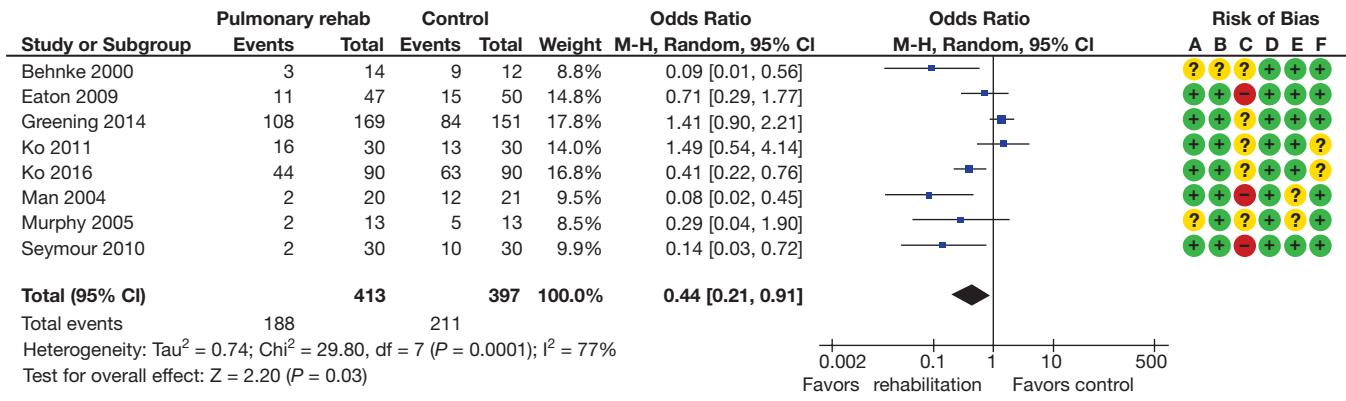


Figure 42-1 Meta-analysis of the effects of pulmonary rehabilitation, compared with usual care, on hospital readmissions following acute exacerbations of COPD. (Reproduced with permission from Puhan MA,

Gimeno-Santos E, Cates CJ, et al. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2016;12(12):CD005305.)

years. Since these patients have advanced disease with limited life expectancy, the goals in the preoperative period differ from those that typically apply to rehabilitation in chronic lung disease.

The overall goals of pretransplant pulmonary rehabilitation are to maintain function, monitor disease progression, prevent complications, provide education about the underlying lung disease and lung transplantation, and offer psychosocial support for patients and families in coping with the stresses of waiting for a potentially life-saving procedure. Although patients may have some initial improvement in exercise tolerance or endurance as they begin rehabilitation, the primary goal for these patients is to maintain mobility and exercise capacity. Exercise sessions also provide an excellent means to monitor disease progression and to detect, at an earlier

stage, problems that commonly occur (e.g., increased breathlessness or reduced arterial oxygenation with exercise).

The goals of education in the pretransplant period are to teach patients about their underlying lung disease, the transplant procedure itself, and expectations following transplantation. Patients can also be taught techniques for self-care and self-assessment that will be useful before and after surgery. The psychosocial stresses of waiting for transplantation are considerable. Many patients feel as though their lives are “on hold.” Some may have moved away from family and social support networks to live close to the transplant center. Providing support for patients and families during this time, whether through formal group support sessions or informal contact with supportive staff and other patients, helps patients cope better with these problems.

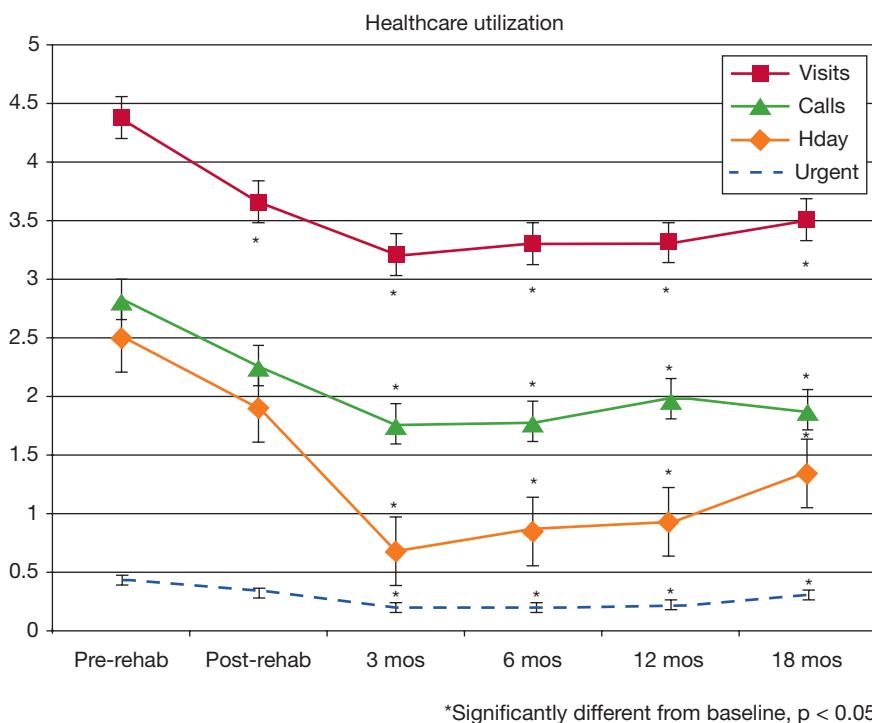


Figure 42-2 Changes in healthcare utilization over 18 months after pulmonary rehabilitation in a collaborative study of 647 patients in 10 centers in California. Results are presented as mean \pm SE. (Reproduced with permission from California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnea, quality of life, and healthcare costs in California. J Cardiopulm Rehabil. 2004;24(1):52–62.)

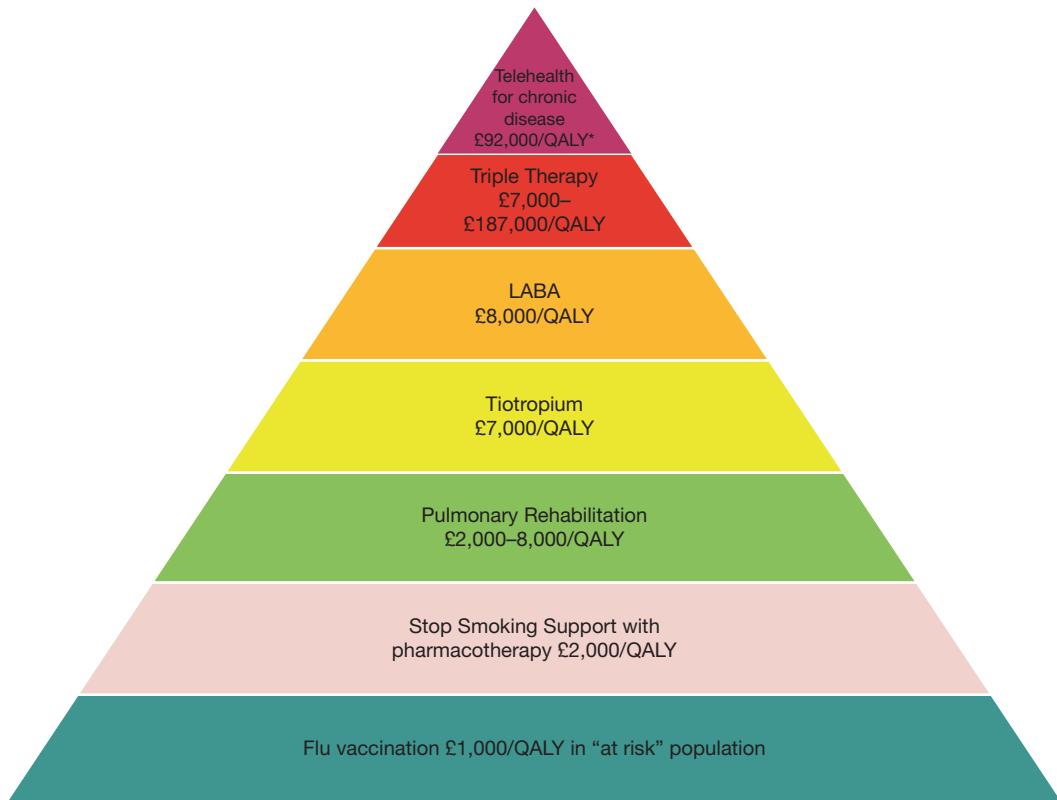


Figure 42-3 Cost-effectiveness of various COPD interventions estimated as cost per quality-adjusted life year (QALY) by the London Respiratory Network with The London School of Economics.

(Reproduced with permission from Ashdown H, Steiner M. Delivering high value therapies in COPD: the secret is in the marketing. *Eur Respir J.* 2019;53(4):1900215.)

■ Posttransplant Rehabilitation

After lung transplantation, patients must learn to cope with a new level of function, new expectations, and a new set of problems. Rehabilitation for patients in this phase can facilitate physical reconditioning, help implement self-care and assessment techniques, and facilitate coping with the psychosocial adaptations to a new lifestyle.

Goals of exercise training after rehabilitation are improved physical work tolerance and continued assessment of symptoms and oxygenation as early warning signs of complications, including rejection and infection. Educational goals are focused on self-care and assessment and the importance of compliance with a new medical regimen. Psychosocial support can assist with adaptation to a new set of stresses related to additional demands and expectations from both patients for themselves and significant others. Patients who are used to being sick, disabled, and cared for by others may now be expected to be well, function independently, return to work, and provide support for others.

■ Lung Volume Reduction Surgery

Among patients with severe emphysema, pulmonary rehabilitation is commonly part of the management plan to optimize them prior to lung volume reduction, either surgically or bronchoscopically, and to facilitate recovery following surgery.^{15,16} Since these patients have severe, disabling chronic lung disease, they are typically good candidates for pulmonary rehabilitation. Enrolling patients in rehabilitation prior to surgery has the advantage of optimizing their functional status, improving physical and psychological symptoms, helping them learn more about their disease and alternative treatment options, and improving their skills for coping and actively co-managing their disease. Patients can then make an informed decision about surgical treatment based upon their optimal level of baseline function. After surgery, similar to the posttransplant

period, rehabilitation helps patients to adapt to new levels of function and to reassess symptoms and oxygenation needs.

■ Rehabilitation After Lung Resection

Patients who undergo pulmonary resection frequently experience a significant increase in symptoms and reduced functional status. This is particularly true for patients with underlying chronic lung disease. Most commonly, surgery is used to treat patients with thoracic neoplasms who are deemed to have resectable disease and are operative candidates. Following resection, these patients with already limited lung function have to learn to adapt to a new, lower level of function. Similar changes may be observed in patients who undergo radiation therapy. Patients in a stable phase of their treatment or in remission may be appropriate candidates for pulmonary rehabilitation. Improvement in health status, physical and psychological symptoms, exercise tolerance, and quality of life—as well as reduced healthcare burdens—are potential benefits. These patients' survival may be as limited by their underlying lung disease as by their treated malignancy.^{8–13}

EXPANDING ACCESS

Despite compelling evidence of benefits, pulmonary rehabilitation is delivered to <5% of eligible patients.^{46,53,54} Limited program availability and geographic disparity among existing programs are significant barriers to broad and equitable delivery of pulmonary rehabilitation.⁵⁵ In addition, insufficient clinician and patient knowledge, patient fear of exercise and rehabilitation, and transportation and social barriers are factors that hinder the uptake of pulmonary rehabilitation.⁵⁴ During the 2020 global COVID-19 pandemic, center-based pulmonary rehabilitation programs were generally unavailable to these high-risk patients due to social distancing recommendations. Alternative models that enable delivery of pulmonary rehabilitation

in the home setting may be important in making this important treatment available to more patients.⁵⁶ The use of telehealth technology to move pulmonary rehabilitation programs away from centers and into patients' homes shows promise.⁵⁷ For example, a randomized controlled trial of 166 patients with COPD assigned to receive 8 weeks of outpatient pulmonary rehabilitation demonstrated non-inferiority for the home-based compared with center-based strategy on the 6-minute walk distance.⁵⁸ Such programs can be remotely delivered using videoconferencing, web-based platforms, mobile phones, and/or telephone with simple and portable exercise equipment.⁵⁹ In addition, these programs may also need to incorporate technology-enabled assessments to individualize exercise therapy, monitor safety, and evaluate effectiveness. While home-based strategies are associated with higher patient adherence,⁶⁰ limited in-person and group contacts may minimize some of the psychosocial benefits that are important features of center-based programs. Nevertheless, telerehabilitation may be necessary in some circumstances.

SUMMARY AND FUTURE OF PULMONARY REHABILITATION

Pulmonary rehabilitation has been well established as a means of improving functional status and reducing the disability and economic burden of the growing number of patients with chronic lung diseases. In adopting a broad rehabilitation medicine perspective, such programs provide interdisciplinary expertise directed toward the needs of the individual disabled patient.

Much of the experience in pulmonary rehabilitation has been in patients with COPD. However, it is clear that similar benefits can result for patients with other disabling chronic pulmonary conditions as well as those recovering from acute processes. Pulmonary rehabilitation may also play an important role in the preoperative evaluation, preparation, and postoperative recovery of patients undergoing surgical procedures, including lung transplantation, lung volume reduction surgery, and lung resection. In many parts of the world, a major challenge for the widespread application of pulmonary rehabilitation to the large number of patients with chronic lung diseases relates to acceptance by health policy makers and health insurers about the benefits and cost savings associated with this treatment. Given the small number of patients who currently have access to pulmonary rehabilitation programs and services, expanding access to the large number of other patients who could benefit is of particular importance. The use of new technologies, such as telemedicine, to reach more patients is particularly appealing, especially following the COVID-19 pandemic that seriously restricted access to the usual outpatient pulmonary rehabilitation centers. It is hoped that, with time and experience, the benefits of pulmonary rehabilitation as an effective, preventive health intervention that can improve patient outcomes and reduce healthcare costs will be better recognized and more widely applied.

REFERENCES

- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2020 report). <http://www.goldcopd.org/>. Accessed July 24, 2020.
- McCarthy B, Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;(2):CD003793.
- Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13–e64.
- American Association of Cardiovascular and Pulmonary Rehabilitation. *Guidelines for Pulmonary Rehabilitation Programs*. Champaign, IL: Human Kinetics; 2011.
- Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest*. 2007;131(5 Suppl):4S–42S.
- Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021.
- Zeng X, Chen H, Ruan H, et al. Effectiveness and safety of exercise training and rehabilitation in pulmonary hypertension: a systematic review and meta-analysis. *J Thorac Dis*. 2020;12(5):2691–2705.
- Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev*. 2017;6:CD012020.
- Granger CL, Parry SM, Edbrooke L, Denehy L. Deterioration in physical activity and function differs according to treatment type in non-small cell lung cancer—future directions for physiotherapy management. *Physiotherapy*. 2016;102(3):256–263.
- Ha D, Ries AL, Lippman SM, Fuster MM. Effects of curative-intent lung cancer therapy on functional exercise capacity and patient-reported outcomes. *Support Care Cancer*. 2020;28(10):4707–4720.
- Quist M, Sommer MS, Vibe-Petersen J, et al. Early initiated postoperative rehabilitation reduces fatigue in patients with operable lung cancer: a randomized trial. *Lung Cancer*. 2018;126:125–132.
- Cavalheri V, Burton C, Formico VR, et al. Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. *Cochrane Database Syst Rev*. 2019;6:CD009955.
- Peddle-McIntyre CJ, Singh F, Thomas R, et al. Exercise training for advanced lung cancer. *Cochrane Database Syst Rev*. 2019;2(2):CD012685.
- Langer D. Lung transplantation. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:409–418.
- Marchetti N, Criner G. Lung volume reduction—old and new approaches. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:419–440.
- Ries AL, Make BJ, Lee SM, et al. The effects of pulmonary rehabilitation in the national emphysema treatment trial. *Chest*. 2005;128(6):3799–3809.
- Vitacca M, Paneroni M, Ambrosino N. Pulmonary rehabilitation in post-acute patients with COVID-19. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:503–510.
- Ries AL, Squier HC. The team concept in pulmonary rehabilitation. In: Fishman AP, ed. *Pulmonary Rehabilitation*. New York, NY: Marcel Dekker; 1996:55–65.
- De Blasio F, Mesquita R, Clini E. The ideal candidate. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:195–202.
- Spruit MA, Pennings HJ, Janssen PP, et al. Extra-pulmonary features in COPD patients entering rehabilitation after stratification for MRC dyspnea grade. *Respir Med*. 2007;101(12):2454–2463.
- Yohannes AM. Anxiety and depression in patients with chronic respiratory disease. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:115–124.
- American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211–277.

23. Ries AL. The role of exercise testing in pulmonary diagnosis. *Clin Chest Med.* 1987;8(1):81–89.
24. Sietsema KE, Sue DY, Stringer WW, Ward SA. *Wasserman & Whipp's Principles of Exercise Testing and Interpretation*. 6th ed. Philadelphia, PA: Wolters Kluwer; 2020.
25. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J.* 2014;44(6):1428–1446.
26. Ries AL, Farrow JT, Clausen JL. Pulmonary function tests cannot predict exercise-induced hypoxemia in chronic obstructive pulmonary disease. *Chest.* 1988;93(3):454–459.
27. Ries AL, Farrow JT, Clausen JL. Accuracy of two ear oximeters at rest and during exercise in pulmonary patients. *Am Rev Respir Dis.* 1985;132(3):685–689.
28. Ries AL, Bullock PJ, Larsen CA, et al. *Shortness of Breath, A Guide to Better Living and Breathing*. St. Louis, MO: Mosby; 2001.
29. Jones AP, Rowe BH. Bronchopulmonary hygiene physical therapy for chronic obstructive pulmonary disease and bronchiectasis. *Cochrane Database Syst Rev.* 2000;(2):CD000045.
30. Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012;(8):CD001287.
31. Breslin EH. Breathing retraining in chronic obstructive pulmonary disease. *J Cardiopulm Rehabil.* 1995;15(1):25–33.
32. Gosselink R. Breathing techniques in patients with chronic obstructive pulmonary disease (COPD). *Chron Respir Dis.* 2004;1(3):163–172.
33. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxic chronic obstructive lung disease: a clinical trial. *Ann Intern Med.* 1980;93(3):391–398.
34. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet.* 1981;1(8222):681–686.
35. Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med.* 2016;375(17):1617–1627.
36. Armstrong M, Crouch R, Vogiatzis I. Modalities of exercise training. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:209–218.
37. Tiep B, Carter R. Oxygen conserving devices and methodologies. *Chron Respir Dis.* 2008;5(2):109–114.
38. Ries AL. The importance of exercise in pulmonary rehabilitation. *Clin Chest Med.* 1994;15(2):327–337.
39. O'Shea SD, Taylor NF, Paratz JD. Progressive resistance exercise improves muscle strength and may improve elements of performance of daily activities for people with COPD: a systematic review. *Chest.* 2009;136(5):1269–1283.
40. Punzal PA, Ries AL, Kaplan RM, Prewitt LM. Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. *Chest.* 1991;100(3):618–623.
41. Carter R, Nicotra B, Clark L, et al. Exercise conditioning in the rehabilitation of patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil.* 1988;69(2):118–122.
42. Costi S, Crisafulli E, Degli Antoni F, et al. Effects of unsupported upper extremity exercise training in patients with COPD: a randomized clinical trial. *Chest.* 2009;136(2):387–395.
43. Man WD, Polkey MI, Donaldson N, et al. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ.* 2004;329(7476):1209.
44. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2016;12:CD005305.
45. Ryrsø CK, Godtfredsen NS, Kofod LM, et al. Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis. *BMC Pulm Med.* 2018;18(1):154.
46. Lindenauer PK, Stefan MS, Pekow PS, et al. Association between initiation of pulmonary rehabilitation after hospitalization for COPD and 1-year survival among Medicare beneficiaries. *JAMA.* 2020;323(18):1813–1823.
47. Man WD, Nolan CM, Puhan MA. Early rehabilitation following exacerbation of COPD. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:241–246.
48. Ibrahim W, Harvey-Dunstan TC, Greening NJ. Rehabilitation in chronic respiratory diseases: in-hospital and post-exacerbation pulmonary rehabilitation. *Respirology.* 2019;24(9):889–898.
49. Griffiths TL, Phillips CJ, Davies S, et al. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. *Thorax.* 2001;56(10):779–784.
50. California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnea, quality of life, and healthcare costs in California. *J Cardiopulm Rehabil.* 2004;24(1):52–62.
51. Raskin J, Spiegler P, McCusker C, et al. The effect of pulmonary rehabilitation on healthcare utilization in chronic obstructive pulmonary disease: The Northeast Pulmonary Rehabilitation Consortium. *J Cardiopulm Rehabil.* 2006;26(4):231–236.
52. Zoumot Z, Jordan S, Hopkinson NS. Emphysema: time to say farewell to therapeutic nihilism. *Thorax.* 2014;69(11):973–975.
53. Vercammen-Grandjean C, Schopfer DW, Zhang N, Whooley MA. Participation in pulmonary rehabilitation by Veterans Health Administration and Medicare beneficiaries after hospitalization for chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev.* 2018;38(6):406–410.
54. Nici L, Singh SJ, Holland AE, ZuWallack RL. Opportunities and challenges in expanding pulmonary rehabilitation into the home and community. *Am J Respir Crit Care Med.* 2019;200(7):822–827.
55. Moscovice IS, Casey MM, Wu Z. Disparities in geographic access to hospital outpatient pulmonary rehabilitation programs in the United States. *Chest.* 2019;156(2):308–315.
56. Singh SJ, Houchen-Wolloff L. Home rehabilitation. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:257–270.
57. Vitacca M, Stickland MK. Telerehabilitation. In: Donner CF, Ambrosino N, Goldstein RS, eds. *Pulmonary Rehabilitation*. 2nd ed. Boca Raton, FL: CRC Press; 2021:271–280.
58. Holland AE, Mahal A, Hill CJ, et al. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. *Thorax.* 2017;72(1):57–65.
59. Bhatt SP, Patel SB, Anderson EM, et al. Video telehealth pulmonary rehabilitation intervention in chronic obstructive pulmonary disease reduces 30-day readmissions. *Am J Respir Crit Care Med.* 2019;200(4):511–513.
60. Hwang R, Bruning J, Morris N, et al. A systematic review of the effects of telerehabilitation in patients with cardiopulmonary diseases. *J Cardiopulm Rehabil Prev.* 2015;35(6):380–389.